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ORIGINAL RESEARCH

Micropulse Laser versus Eplerenone for Chronic Central Serous Chorioretinopathy: A 12-Month Comparison

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ABSTRACT

***Introduction*:** To compare the long-term efficacy of navigated subthreshold micropulse laser (NSML) and continuous oral eplerenone (EPL) in chronic central serous chorioretinopathy (cCSC).

***Methods*:** This retrospective observational study included 44 eyes with cCSC (EPL: $n=26$; NSML: $n=18$). Best-corrected visual acuity (BCVA), central macular thickness (CMT), subretinal fluid (SRF) height, and subfoveal choroidal thickness (SFCT) were evaluated over 12 months.

***Results*:** Both groups showed significant improvements in BCVA and CMT ($p<0.05$). Complete SRF resolution was achieved in both groups by 12 months, with NSML showing faster resolution (2.77 ± 1.43 vs. 6.34 ± 2.17 months, $p<0.001$). The EPL group demonstrated significant SFCT reduction at 6 and 12 months ($p=0.001$), while the NSML group showed no significant SFCT changes ($p>0.05$).

***Conclusions*:** Both NSML and EPL improved retinal morphology and visual function in patients with cCSC. NSML achieved faster SRF resolution, while EPL resulted in more significant choroidal thickness reduction. These findings suggest distinct mechanisms of action: NSML primarily affects the retinal pigment epithelium, while EPL modulates choroidal vasculature. Treatment choice may depend on individual patient characteristics and treatment goals.

Keywords: Optical coherence tomography; OCT; Central serous chorioretinopathy; Pachychoroid; Subfoveal choroidal thickness

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Key Summary Points

Why carry out this study?

Chronic central serous chorioretinopathy (cCSC) management remains challenging, with ongoing debates about optimal treatment strategies.

A direct comparison between navigated subthreshold micropulse laser (NSML) and continuous oral eplerenone (EPL) was lacking in the literature, hindering evidence-based decision-making for clinicians.

What was learned from the study?

Both NSML and EPL demonstrated effectiveness in improving retinal morphology and visual function in patients with cCSC over a 12-month period.

NSML achieved faster subretinal fluid resolution (2.77 ± 1.43 versus 6.34 ± 2.17 months, $p < 0.001$), potentially offering quicker visual recovery.

EPL showed a more pronounced and sustained effect on reducing subfoveal choroidal thickness, suggesting its potential for long-term disease management.

The distinct advantages of each treatment suggest that therapy choice may need to be tailored to individual patient characteristics and treatment goals in cCSC management.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a significant macular disease characterized by the detachment of the neurosensory retina, often accompanied by pigment epithelium detachment (PED) [1, 2]. Although the exact pathophysiology of CSC remains poorly understood, it is widely believed to be associated with hyperpermeability of the choroidal vessels and a compromised external blood–retina barrier [3, 4]. Acute CSC typically resolves within 2–3 months, but 30–50% of patients experience recurrence within a year, and 5–10% develop chronic CSC (cCSC), defined by persistent subretinal fluid (SRF) exceeding 4–6 months [5, 6].

A recent proposal by Chhablani et al. [7] has introduced a revised classification system for CSC, which divides it into two subcategories: simple and complex. This categorization is based primarily on the presence of serous retinal detachment and alterations in the retinal pigment epithelium (RPE) [7]. The new classification aims to provide a more detailed understanding of the different presentations and characteristics of CSC cases.

Verteporfin photodynamic therapy (PDT) remains the primary treatment for CSC, despite potential adverse effects such as RPE atrophy, choroidal ischemia, and the development of macular neovascularization (MNV) [8–12]. Alternative approaches include mineralocorticoid receptor (MR) inhibitors like eplerenone (EPL) [13–16]. However, in recent years, the effectiveness of MR inhibitors has become a subject of controversy, particularly regarding their short-term use [17–19].

Subthreshold micropulse laser (SML) has been proposed as a potentially effective approach for the treatment of cCSC [20]. This technique targets the RPE using short-duration, subthreshold laser spots. The stimulation induces the production of heat shock proteins, which protect cells from stress by inhibiting inflammatory and apoptotic pathways [21, 22]. By normalizing the RPE function, SML treatment has been shown to facilitate the reabsorption of SRF [23]. Recent advancements in non-contact navigated systems have further enhanced SML's efficacy and safety. These systems incorporate eye tracking technology, compensating for eye movements and ensuring precise, consistent laser delivery. The navigated SML (NSML) improves treatment targeting through real-time image alignment, potentially leading to better outcomes.

Notably, while both EPL and SML have shown promise in treating cCSC, a direct comparison between these two approaches is lacking in the current literature. This gap in knowledge is significant, as it hinders clinicians' ability to make evidence-based decisions when selecting between these treatment options. A recent comparative study by Mehta et al. [24] further

explored the efficacy of different treatment modalities in cCSC, providing additional context for our current investigation.

This retrospective observational study aims to compare anatomical and functional changes in cCSC-affected eyes treated with multiple sessions of navigated 577-nm yellow SML versus continuous oral EPL over a 12-month follow-up period. By directly comparing these treatments, we seek to provide valuable insights that can inform clinical decision-making and potentially improve patient outcomes in the management of cCSC.

METHODS

Study Participants

This retrospective observational comparative study was conducted across two centers, involving 44 eyes from 44 consecutive patients with unilateral exudative cCSC. Patients were enrolled consecutively at each center based on the treatment modality available: the EPL group, consisting of 26 eyes treated with continuous oral EPL, was enrolled at the University of Bari "Aldo Moro," while the SML group, comprising 18 eyes treated with NSML using the Navilas® 577s system, was enrolled at the University of "G. d'Annunzio" in Chieti-Pescara. The division of treatments between centers was based on the specific expertise and equipment available at each institution, with the University of Bari specializing in pharmacological management and the University of Chieti-Pescara having advanced laser treatment capabilities. This retrospective study was conducted between January 2021 and May 2023 in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. In Italy, retrospective studies using anonymized data do not require specific patient consent or ethical committee approval. However, this study was reviewed and approved by the internal review boards of the University of Bari "Aldo Moro" and the University of "G. d'Annunzio" Chieti-Pescara. Despite the retrospective nature of the study, informed consent was obtained from all participants for the use of their clinical data for research purposes.

For this study, unilateral exudative cCSC was defined as the presence of SRF for over 6 months. Treatment success was defined as complete SRF resolution.

Inclusion criteria for the study were as follows: patients aged 18 years or older, with a disease duration of 6 months or more, the presence of foveal SRF confirmed by spectral-domain optical coherence tomography (SD-OCT), and no prior treatment for cCSC. This study focused on patients receiving their first treatment for cCSC.

Patients were excluded from the study if they had undergone previous ophthalmological surgery, laser therapy, or PDT. Additionally, those with a history of anti-vascular endothelial growth factor (VEGF) treatment, presence of MNV assessed with OCT angiography (OCTA) and indocyanine green angiography (ICGA), systemic contraindications to MR inhibitor administration, systemic steroid use, other retinal disorders, or pregnancy were not included in the study.

Examinations

Each patient underwent a complete ophthalmological evaluation, including measurement of best-corrected visual acuity (BCVA) and intraocular pressure (IOP), and a dilated fundus examination with fundus autofluorescence (FAF), fundus fluorescein angiography (FFA), ICGA, structural OCT, and OCTA. SD-OCT examinations were performed using Spectralis® HRA+OCT (Heidelberg Engineering; Heidelberg, Germany). OCTA was consistently used to screen all participants for the presence of MNV [25].

Data analysis was conducted at three time points: baseline, 6-month follow-up, and 12-month follow-up. FFA, ICGA, and OCTA were performed at baseline. The hyperpermeability of the choroidal vessels was examined in the late phase of ICGA as multifocal areas of hyperfluorescence with blurred margins [26].

OCT Imaging Analysis

SD-OCT images of the macular area were obtained with 49 horizontal raster dense linear B-scans centered on the fovea. The enhanced depth imaging (EDI) mode was applied in all patients [27].

Central macular thickness (CMT). CMT measurements were automatically averaged within the 1-mm-diameter central fovea subfield of the ETDRS (Early Treatment Diabetic Retinopathy Study) thickness map [28].

Subretinal fluid height (SRF). SRF was evaluated using the inbuilt manual caliper as the vertical distance between the external limiting membrane and RPE at the foveal center [29].

Subfoveal choroidal thickness (SFCT). SFCT was measured with the caliper function of structural OCT. The SFCT was measured from Bruch's membrane to the chorio–scleral interface perpendicularly in the center of the fovea [30].

Outcome Measures

The main outcome measures were (i) BCVA (logMAR scale), (ii) central macular thickness, (iii) SRF height, and (iv) SFCT. These measurements were obtained at baseline and at each follow-up visit to evaluate the changes and trends in these parameters over time.

Eplerenone Treatment

In accordance with our previous publication [31], all patients in this study received a daily dosage of 50 mg of EPL. The administration of EPL began after obtaining approval from the patients' general practitioners. Throughout the study period, we closely monitored the potassium levels of the participants. All patients were able to maintain EPL therapy, as the observed adverse events were not deemed significant.

577-nm Micropulse Laser Treatment

A Navilas® Laser System 577s Prime, a 577-nm yellow laser system (OD-OS GmbH, Teltow, Germany), was used. Prior to laser photocoagulation, mid-phase FFA and mid-phase ICGA images of the posterior pole were captured. The selected images showing the focal leakage were imported and automatically superimposed on the actual image captured. The micropulse parameters were set for all patients, with a spot size of 100 µm and a duration of 100 ms with 5% duty cycle. The power was individualized in every patient after energy titration before treatment in a normal area of the retina outside the vascular arcade. The titration was performed in microsecond mode with a 5% duty cycle starting from 700 mW power with single spots with 50 mW increasing power until the appearance of a barely visible burn on the retina; this was used as the threshold limit. The final laser treatment power was set at 30% of titrated energy. A multiple dense spot pattern was set and delivered to the leakage areas on the mid-phase FFA or mid-phase ICGA images, which were aligned with the live image by means of an eye tracking system.

If SRF persisted during the 90-day follow-up visit, patients were recommended for a second SML treatment, utilizing the same parameters of individualized power adjusted through energy titration for each patient, and the power was set at 30% of titrated energy. Additionally, no treatment was administered in the foveal region.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Quantitative variables were reported as mean ± standard deviation (SD). Given the relatively small sample size, particularly in the NSML group ($n = 18$), we adopted a conservative approach using nonparametric tests as our primary analysis method. Given the retrospective nature of our study, we conducted a post hoc power analysis to assess the adequacy of our sample size. Using G*Power software (version 3.1.9.7), we determined that our sample size of 44 (EPL: $n = 26$; NSML: $n = 18$) provided 81% power to detect a large effect size (Cohen's $d = 0.8$) difference between groups at a significance level of 0.05. The Shapiro–Wilk test was

used to assess the normality of data distribution. However, due to the limited sample size and to ensure robustness of our analyses, we opted for nonparametric tests regardless of the Shapiro–Wilk results. For within-group comparisons over time (baseline, 6 months, and 12 months), we used the Friedman test. When the Friedman test showed significant differences, post hoc analyses were conducted using Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons. For between-group comparisons at each time point, we employed the Mann–Whitney *U* test. To analyze changes over time between groups, we calculated the delta changes (differences between time points) for each outcome measure (BCVA, CMT, SRF, and SFCT). These delta changes were then compared between the EPL and NSML groups using the Mann–Whitney *U* test. A p value < 0.05 was considered statistically significant.

RESULTS

Characteristics of Patients Included in the Analysis

A total of 44 eyes from 44 patients with cCSC were evaluated, with 26 patients (59.1%) in the EPL-treated group and 18 (40.9%) in the NSML-treated group. The groups included 38 men (86.4%) and six women (13.6%). Twenty-six patients were treated with oral EPL (59.1%) and 18 (40.9%) were treated with NSML. The mean (±SD) age was 46.23 ± 10.57 years in the EPL group and 51.11 ± 9.08 in the NSML group ($p = 0.632$). None of them received steroid therapy. The average duration of symptoms with fundus and OCT evidence of SRF persistence was 6.61 ± 0.76 months in patients treated with EPL (range from 5.5 to 8 months) and 6.55 ± 0.72 months in patients treated with NSML (range from 5.5 to 8.5 months). All patients presented choroidal hyperpermeability. The mean number of NSML treatment sessions was 1.55 ± 0.51 (range 1–2), which included both initial treatment and repeat treatment due to recurrence. Characteristics of subjects included in the analysis are shown in Table 1.

Treatment Response

BCVA. The mean BCVA was 0.23 ± 0.20 logMAR in patients treated with EPL and 0.22 ± 0.14 in patients treated with NSML at baseline. Compared with baseline, BCVA was significantly improved at follow-up examinations in both the EPL group (6 months: 0.06 ± 0.09 logMAR, $p < 0.001$; 12 months: 0.05 ± 0.08 logMAR, $p < 0.001$) and the NSML group (6 months: 0.07 ± 0.08 logMAR, $p = 0.002$; 12 months: 0.04 ± 0.07 logMAR, $p < 0.001$) (Table 2). No differences in BCVA were observed between the two groups at different follow-up visits ($p > 0.05$) (Table 3).

Central macular thickness. Comparing the measurements with the baseline, we observed a significant reduction in CMT at the 6-month and 12-month follow-up assessments. At baseline, the mean CMT was 390 ± 155 µm in the EPL group and 359 ± 101 µm in the SML group. Following the initiation of therapy, both the EPL group and the NSML group exhibited a decrease in CMT. In the EPL group, the CMT measurements at 6 months were 182 ± 50 µm ($p < 0.001$) and at 12 months were 164 ± 56 µm ($p < 0.001$). In the NSML group, the CMT measurements at 6 months were 221 ± 38 µm ($p = 0.001$) and at 12 months were 194 ± 18 µm ($p = 0.004$). (Table 2). Moreover, no differences in CMT were observed between the two groups at different follow-up visits ($p > 0.05$) (Table 3).

Subretinal fluid. Both the EPL group and the NSML group demonstrated complete reabsorption of SRF at the 12-month follow-up. In the EPL group, there was a significant SRF decrease from 208 ± 155 µm at baseline to 25 ± 44 µm at 6 months ($p < 0.001$), and complete reabsorption was observed at 12 months ($p < 0.001$). In the NSML group, there was also a significant decrease in SRF from a baseline measurement of 144 ± 108 µm to complete resolution at 6 months ($p = 0.002$). This resolution was maintained at the 12-month follow-up ($p = 0.002$). No differences were found between the two groups (Table 3).

These findings suggest that both treatment modalities, EPL and NSML, were effective in promoting the reabsorption of SRF, with the

Table 1 The clinical and medical characteristics of patients included in the analysis

Variables	EPL ($n=26$)	NSML ($n=18$)	p value
Age (years)	46.23 ± 10.57	51.11 ± 9.08	0.632
Female gender (n, %)	4 (15%)	2 (11%)	0.455
cCSC duration (months)	6.61 ± 0.76	6.55 ± 0.72	0.411
Hypertension, n (%)	4 (15%)	3 (17%)	0.455
Focal RPE atrophy, n (%)	3 (12%)	2 (11%)	0.482
PED, n (%)	7 (27%)	4 (22%)	0.365
Intraretinal fluid at baseline, n (%)	2 (7%)	2 (11%)	0.353
Foveal SRF, n (%)	26 (100%)	18 (100%)	1.000
SFCT at baseline	502.1 ± 134	426.7 ± 71	0.017
Steroid use, n (%)	0 (0)	0 (0)	1.000

Baseline clinical characteristics of patients

cCSC chronic central serous chorioretinopathy, *CH* choroidal hyperpermeability, *EPL* eplerenone, *NSML* navigated subthreshold microsecond pulse laser, *PED* pigment epithelium detachment, *RPE* retinal pigment epithelium, *SFCT* subfoveal choroidal thickness, *SRF* subretinal fluid

NSML group achieving complete resolution of SRF earlier at 6 months and maintaining it at the 12-month time point (Table 2). Ten patients (55.5%) presenting SRF at the 90-day control visit underwent a second NSML treatment. The mean time for SRF resolution after treatment initiation was 6.34 ± 2.17 months in the EPL group and 2.77 ± 1.43 months in the NSML group, the latter showing a significantly shorter time for SRF resolution ($p<0.001$).

Subfoveal choroidal thickness. In the EPL group, there was a significant decrease in SFCT from 502 ± 134 µm at baseline to 440 ± 115 µm at 6 months ($p=0.001$). This reduction further continued, reaching 406 ± 106 µm at 12 months ($p=0.001$). In contrast, no significant reduction in SFCT was observed in the NSML group at the 6-month ($p=0.020$) or 1-year follow-up ($p=0.041$) (Table 2). Furthermore, the calculated changes in SFCT (Δ baseline–6 months and Δ baseline–12 months) between the two groups exhibited statistically significant differences (Table 3). This indicates that EPL treatment may have a more pronounced effect on choroidal thickness than NSML. These findings are supported by the data presented in Table 3 and Fig. 1.

Safety Analysis

During the study, only mild adverse events were reported in the EPL group, including dizziness and dry mouth, which are known side effects of EPL administration. These adverse events were considered to be tolerable and did not result in any significant complications or adverse effects on potassium levels or creatinine clearance. Therefore, all the patients continued EPL treatment because severe adverse events were not reported.

DISCUSSION

In this retrospective observational study, we compared the long-term efficacy of NSML and EPL in patients with cCSC over a 12-month follow-up period. Our study design, involving two specialized centers, reflects the real-world clinical scenario where different institutions may focus on specific treatment modalities. While this approach allowed us to leverage specialized expertise and equipment, we acknowledge the

Table 2 Functional and anatomical (OCT) outcomes in EPL and NSML groups: data and comparisons

		Baseline	6 months	12 months
BCVA (logMAR)	EPL	0.23 ± 0.20	0.06 ± 0.09 $p < 0.001$[a]	0.05 ± 0.08 $p < 0.001$[a] $p = 0.161$[b]
	NSML	0.22 ± 0.14	0.07 ± 0.08 $p = 0.002$[a]	0.04 ± 0.07 $p < 0.001$[a] $p = 0.128$[b]
CMT (μm)	EPL	390 ± 155	182 ± 50 $p < 0.001$[a]	164 ± 56 $p < 0.001$[a] $p = 0.221$[b]
	NSML	359 ± 101	221 ± 38 $p = 0.001$[a]	194 ± 18 $p = 0.004$[a] p = 0.073[b]
SRF (μm)	EPL	208 ± 155	25 ± 44 $p < 0.001$[a]	0.0 ± 0.0 $p < 0.001$[a] $p = 0.043$[b]
	NSML	144 ± 108	0.0 ± 0.0 $p = 0.002$[a]	0.0 ± 0.0 $p = 0.002$[a] $p > 0.05$[b]
SFCT (μm)	EPL	502 ± 134	440 ± 115 $p = 0.001$[a]	406 ± 106 $p = 0.001$[a] $p = 0.038$[b]
	NSML	426 ± 71	416 ± 69 $p = 0.020$[a]	411 ± 46 $p = 0.041$[a] $p = 0.286$[b]

Data are presented as mean ± SD. *P* values represent significance of comparison to baseline data of visual and anatomical parameters at each time point. [a]Comparison with baseline; [b]comparison with 6 months

BCVA best-corrected visual acuity, *CMT* central macular thickness, *EPL* eplerenone group, *NSML* navigated subthreshold microsecond pulse laser, *OCT* optical coherence tomography, *SFCT* subfoveal choroidal thickness, *SRF* subretinal fluid

potential for bias, which we sought to mitigate through consecutive patient enrollment and uniform inclusion/exclusion criteria across both groups.

Both EPL and NSML treatments demonstrated effectiveness in improving retinal morphology and visual function, as evidenced by significant reductions in CMT, complete reabsorption of SRF, and improvements in BCVA. Interestingly, our results revealed distinct advantages for each treatment modality. The NSML group showed a more rapid resolution of SRF, with a higher percentage of patients achieving complete fluid resolution at the 6-month mark. This suggests that NSML may have a faster onset of action in addressing SRF accumulation. In contrast, EPL treatment exhibited a more pronounced and sustained effect on reducing SFCT. The changes in SFCT observed in the NSML group were comparatively transient, indicating that EPL may be more effective in modulating choroidal thickness over the long term. This finding highlights

Table 3 Comparison of EPL group versus NSML group

	EPL group (*n* = 26)	**NSML group (*n* = 18)**	***P* value**
Δ BCVA (logMAR)	Δ baseline–6 months 50.7 ± 52.9	Δ baseline–6 months 53.8 ± 71.7	0.869
	Δ baseline–12 months 54.8 ± 56.1	Δ baseline–12 months 80.9 ± 80.3	0.210
	Δ 6 months–12 months 2.3 ± 5.7	Δ 6 months–12 months 11.2 ± 11.4	0.111
Δ CMT	Δ baseline–6 months −49.5 ± 18.6	Δ baseline–6 months −33.3 ± 21.2	0.067
	Δ baseline–12 months −55.1 ± 18.3	Δ baseline–12 months −41.1 ± 18.5	0.085
	Δ 6 months–12 months −9.2 ± 17.6	Δ 6 months–12 months 10.7 ± 11.1	0.751
Δ SRF	Δ baseline–6 months −85.7 ± 23.4	Δ baseline–6 months −100 ± 0.0	0.082
	Δ baseline–12 months −100 ± 0.0	Δ baseline–12 months −100 ± 0.0	–
	Δ 6 months–12 months −100 ± 0.0	Δ 6 months–12 months 0.0 ± 0.0	–
Δ SFCT	Δ baseline–6 months −12.2 ± −13.5	Δ baseline–6 months 2.4 ± 5.4	0.083
	Δ baseline–12 months −19.1 ± −20.3	Δ baseline–12 months −2.7 ± 6.6	< 0.001
	Δ 6 months–12 months −7.8 ± −7.9	Δ 6 months–12 months −0.2 ± 7.2	0.034

Data are presented as mean ± SD

Friedman nonparametric test was performed to obtain *p* values

BCVA best-corrected visual acuity, *CMT* central macular thickness, *EPL* eplerenone group, *NSML* navigated subthreshold microsecond pulse laser, *SFCT* subfoveal choroidal thickness, *SRF* subretinal fluid

EPL's potential in addressing the choroidal component of cCSC pathophysiology.

To date, either half-dose or half-fluence PDT is considered the gold standard treatment for patients with cCSC [2]. OCTA studies indicate that following the use of PDT, there is a notable reperfusion of the choriocapillaris evident as early as 1 month post-treatment [10,11]. Nevertheless, PDT is associated with potential adverse effects, such as choroidal and choriocapillaris ischemia, RPE atrophy, and choroidal neovascularization (CNV) development [12, 32–34]. These complications have raised concerns about the long-term safety of PDT. In light of these concerns, alternative treatment options such as NSML and MR inhibitors have emerged as viable alternatives for cCSC management.

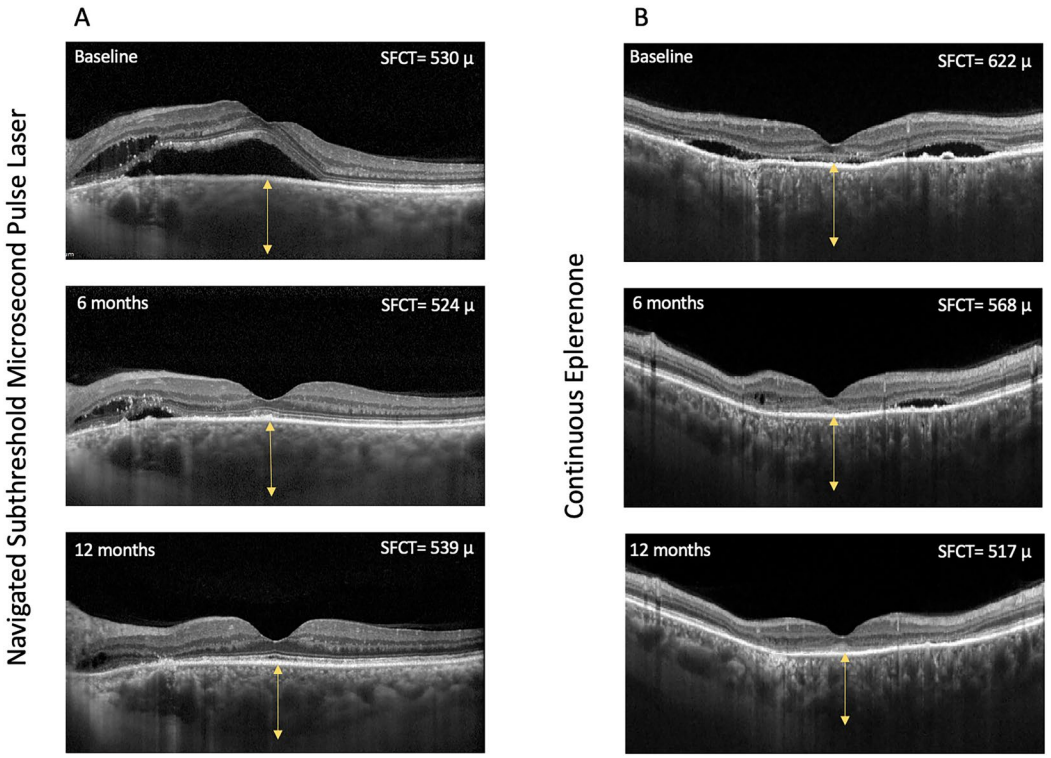

Fig. 1 The changes in subfoveal choroidal thickness (SFCT) in both groups. In the case of patients with chronic central serous chorioretinopathy (cCSC) treated with navigated subthreshold microsecond pulse laser (NSML), no significant reduction in SFCT was observed at the 6-month or 1-year follow-up (**A**). On the other hand, patients with cCSC treated with continuous EPL (50 mg/daily) showed a significant decrease in SFCT at 6 months, and this reduction continued even further at 12 months (**B**)

As stated above, the efficacy of NSML is supposed to be related to the RPE absorption of laser energy of visible wavelengths, with a consequent recovery of RPE cell functionality [35]. Overall, the main advantage is the SRF resolution without significant retinal or choroidal lesions or other side effects [36]. Several authors have previously reported the effectiveness of NSML in the treatment of cCSC. The study by Scholz et al. in 2015 evaluated the efficacy of SML in patients with cCSC who were resistant to PDT. The study had a mean follow-up period of 5.0±3.7 months and included a variable number of SML treatments ranging from one to three sessions. The results of the study showed that 24% of the patients achieved complete resolution of SRF, indicating a successful outcome. Additionally, 75% of the patients experienced at least partial resolution of fluid, demonstrating a positive response to the SML treatment [37]. In a recent study conducted by Sun et al. [38], similar percentages of resolution were observed. The study reported a rate of resolution after one application of NSML of 63.63% in patients with cCSC who had SRF involving the macula center within a 6-month time frame. The study further indicated that SRF was completely resolved in approximately 50% of patients by week 3 and 65% of patients by week 12. Indeed, Luttrull et al. [39] conducted a study in which they observed a remarkable 100% resolution rate among 11 patients who underwent SML treatment, regardless of the duration of the disease prior to the treatment. The noteworthy aspect is that this complete resolution of fluid was achieved with just a single session of SML. However, our study differs, as we achieved similar results using multiple sessions of SML. In support of this approach, Kim and colleagues reported that multiple-session NSML treatment

could be advantageous for the long-term management of cCSC [20]. Based on the parameters provided, including a spot diameter of 100 µm, 20-ms duration, 15% duty cycle, and low power ranging from 200 to 400 mW, the authors suggested that delivering short-duration treatment over multiple sessions using these SML settings can be a viable approach for achieving effective and safe treatment of chronic and recurrent CSC over the long term.

Similarly, multiple authors have reported positive outcomes with EPL for the treatment of cCSC. Bousquet and coworkers reported a significant reduction in SRF levels and an improvement in visual acuity after the oral administration of EPL for 1 to 3 months [40]. In a separate study, Gergely et al. followed a group of 28 patients with bilateral cCSC for 6 months, administering 50 mg/day of EPL orally for 3 months. They observed a decrease in macular and choroidal thickness in all eyes at 3 months, along with an improvement in BCVA [41]. While our results demonstrate a sustained effect of EPL on choroidal thickness, it is important to note the potential for a rebound effect upon drug discontinuation [42]. However, these studies often had limitations in terms of sample size and duration of follow-up. In contrast, our approach involved treating all patients with long-term EPL intake (50 mg/day), similar to our previous research [31].

When comparing the two treatment modalities, we found that both achieved the same rate of SRF resolution, but with different timing. Specifically, patients treated with multiple sessions of NSML experienced faster resolution of SRF than the group treated with EPL. However, there was no statistically significant difference in visual acuity between the two groups. Furthermore, it appears that NSML therapy demonstrates greater effectiveness in targeting the RPE, promoting fluid reabsorption. Conversely, EPL demonstrates efficacy in reducing the dilation of choroidal vessels over the long term, thereby contributing to a reduction in their overall thickness.

The differential effects observed between EPL and NSML can be attributed to their distinct mechanisms of action. EPL, as an MR antagonist, likely exerts its effects primarily on the choroidal vasculature. By inhibiting the action of aldosterone on MRs in the choroidal vessels, EPL may reduce choroidal hyperpermeability and vasodilation, leading to a more pronounced and sustained reduction in choroidal thickness [43]. This mechanism explains the significant decrease in SFCT observed in the EPL group. In contrast, NSML's primary target is the RPE. The subthreshold laser energy absorbed by the RPE stimulates the production of heat shock proteins and other factors that enhance RPE function, including its fluid pumping capacity [36, 38]. This direct action on the RPE likely accounts for the faster resolution of SRF observed in the NSML group. However, as NSML does not directly address the choroidal component of cCSC, its effects on choroidal thickness are less pronounced and more transient than those of EPL.

These findings have important clinical implications for the management of cCSC. NSML might be the preferred initial treatment in cases where rapid visual recovery is crucial, such as in patients with significant work or lifestyle impairment due to acute vision loss. The faster SRF resolution with NSML could lead to quicker visual improvement and patient satisfaction. On the other hand, EPL might be more suitable for patients with a prominent choroidal component or recurrent disease, or in cases where long-term disease control is the primary goal. The sustained effect of EPL on choroidal thickness suggests it might be more effective in preventing disease recurrence. Importantly, our results also suggest the potential benefit of a combination or sequential approach using both NSML and EPL. Given that NSML demonstrates a rapid effect on SRF resolution while EPL shows a more sustained impact on choroidal thickness, a combined treatment strategy could offer synergistic benefits. For instance, NSML could be used as an initial treatment to achieve rapid fluid resolution and visual improvement, followed by EPL to maintain the treatment effect and potentially prevent recurrence by addressing the underlying choroidal pathology. This approach might be particularly beneficial in patients with chronic or recurrent cCSC, where both immediate symptom relief and long-term disease control are important.

Our study has several limitations that should be considered when interpreting the results. Firstly, the retrospective nature of the study introduces potential for selection bias. Moreover, the allocation of treatments between centers, while reflecting real-world practice, may have introduced bias due to potential differences in patient populations or care protocols. Although we attempted to mitigate this through strict inclusion criteria and consecutive enrollment, center-specific factors could have influenced our outcomes, highlighting the need for future randomized multicenter trials. Furthermore, our relatively small sample size, particularly in the NSML group, limited our ability to perform meaningful subgroup or matched-pair analyses to account for potential confounding factors. The imbalance in group sizes (26 in the EPL group vs. 18 in the NSML group) could have affected the statistical power of our analyses. While our 12-month follow-up provides valuable information on treatment efficacy, longer-term studies are needed to fully assess safety profiles and recurrence rates for both NSML and EPL. Larger, randomized controlled trials, with a longer follow-up period, are necessary to confirm our preliminary results, and would be beneficial to evaluate the durability of treatment effects, particularly for EPL's impact on choroidal thickness. Lastly, our study focused on specific outcome measures including BCVA, CMT, SRF, and SFCT. While these are important indicators of treatment efficacy, future studies could benefit from including additional functional measures, quality of life assessments, and more detailed analysis of choroidal and RPE changes using advanced imaging techniques. Despite these limitations, however, our study provides valuable insights into the comparative efficacy of NSML and EPL in the treatment of cCSC.

CONCLUSION

In conclusion, our study provides valuable insights into the comparative efficacy of NSML and EPL in the treatment of cCSC. Both treatments demonstrated effectiveness in improving retinal morphology and visual function, but with distinct advantages. NSML showed a more rapid resolution of SRF, potentially offering quicker visual recovery, while EPL demonstrated a more pronounced and sustained effect on choroidal thickness, suggesting its potential for long-term disease management. These findings highlight the complex nature of cCSC and suggest that treatment strategies may need to be tailored to individual patient characteristics and treatment goals. Further research, particularly randomized prospective trials, is necessary to validate the effectiveness of these therapies in the management of cCSC.

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

Declarations

Conflict of Interest. Pasquale Viggiano, Giacomo Boscia, Enrico Borrelli, Federica Evangelista, Maria Oliva Grassi, Ermete Giancipoli,

Rodolfo Mastropasqua, Alberto Quarta, Raffaella Aloia, Giovanni Alessio, Lisa Toto, and Francesco Boscia declare that they have no conflict of interest.

Ethical Approval. This retrospective study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments between January 2021 and May 2023. In Italy, retrospective studies using anonymized data do not require specific patient consent or ethical committee approval. However, this study was reviewed and approved by the internal review boards of the University of Bari "Aldo Moro" and the University of "G. d'Annunzio" Chieti-Pescara. Despite the retrospective nature of the study, informed consent was obtained from all participants for the use of their clinical data for research purposes.

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