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Case Series

SUBTHRESHOLD LASER AS ALTERNATIVE TREATMENT FOR CHRONIC CENTRAL SEROUS CHORIORETINOPATHY - A CASE SERIES

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ABSTRACT

Introduction: Subthreshold laser is a relatively new and promising therapy for chronic central serous chorioretinopathy (CSCR), particularly in regions where current mainstay therapy in the form of Indocyanine green (ICG)-based photodynamic therapy (PDT) is either too expensive or unavailable. We reported the clinical efficacy of the nondamaging subthreshold laser therapy for chronic CSCR using Endpoint Management™ system.

M**ethods**: This retrospective, non-randomized, interventional case series included 13 eyes with chronic CSCR (more 3 months duration) treated at JEC Eye Hospitals, Jakarta (January 2023-January 2024). Patients underwent 577-nm subthreshold laser therapy using PASCAL® (Topcon Medical Laser System) Streamline with 200 µm retinal spot sizes. Using Endpoint Management™ Software, the laser power was first titrated with 15-ms pulses at 30% pulse energy and 0.25 spot spacing, applied over serous retinal detachment and adjacent non-thickened retina. Subretinal fluid (SRF) was measured on OCT (CIRRUS™ HD-OCT, Carl Zeiss Meditec, Inc). Primary outcomes included SRF changes and best-corrected visual acuity (BCVA) assessed at 3 months. Secondary outcome was the presence or absence of metamorphopsia.

Results: Thirteen eyes from 13 patients with chronic CSCR (mean age: 42.6 ± 10.04 years; 92.3% male) were included. Median symptom duration was 12 (4-24) months, and all presented with metamorphopsia. Laser therapy used 288 ± 95.36 shots at 122.50 ± 11.65 mW. Twelve eyes (92.31%) showed SRF reduction from mean 206.9 ± 90.86 µm at baseline to median 16 (0-154) µm at final visit, with six eyes (46.1%) achieving complete resolution at 12.5 (7-14) weeks. Twelve eyes (92.31%) had also improved or stable visual outcomes with mean BCVA improving from 0.74±0.26 at baseline to median 1.0 (0.1-1.0) at final visit, and 10 eyes (76.9%) achieved BCVA of 1.0.

Conclusion: Subthreshold therapy using Pascal laser with Endpoint Management was associated with improved visual acuity and reduced SRF in chronic CSCR. However, the small sample size and short follow-up limit definitive conclusions regarding long-term efficacy. Further comparative studies are needed to establish its role relative to conventional laser photocoagulation and anti–vascular endothelial growth factor therapy.

Keywords: central serous chorioretinopathy, CSCR, subthreshold laser, endpoint management, subretinal fluid

Introduction

Central serous chorioretinopathy (CSCR) is the fourth most common nonsurgical retinopathy behind age-related macular degeneration, diabetic retinopathy, and branch retinal vein occlusion. It affects roughly 10 men and 2 women per 100,000 people.[1,2] The pathophysiology of CSCR has been attributed to hyperpermeable choroidal vessels, impaired choroidal vascular autoregulation, and dysfunction of the retinal pigment epithelium (RPE) barrier and pumping. It is usually self-limiting with good recovery of visual function. However, 33-50% of cases can have recurrences with long-standing areas of neurosensory detachment with subretinal fluid leading to permanent visual impairment. When subretinal fluid persist longer than 3 months, the term chronic CSCR is generally used.[2] Treatment for CSCR have been sought for many years, with laser photocoagulation of the leakage point representing a practical solution in selected cases of longer duration. However, conventional photocoagulation produces retinal damage, which is unacceptable near the fovea. In addition to this method, practitioners have looked to numerous types of oral medication. However, any results they have obtained have not been confirmed in randomized trials. Photodynamic therapy (PDT) is an important form of treatment of chronic CSCR but this treatment is costly and unavailable in some regions. The efficacy of anti-VEGF treatment for chronic CSCR is disputable, with recent data failing to confirm its superiority over PDT or other therapies.[2-7]

Fundamentally, photothermal therapy is based on conversion of absorbed laser light in the RPE and choroid into heat. In photocoagulation, diffusion of heat from the RPE into retina leads to thermal damage to photoreceptors or, at higher settings, even to the inner retinal cells. While destruction of a significant fraction of photoreceptors, the most metabolically active and numerous cells in the retina, is desirable to reduce metabolic load and thereby decrease secretion of angiogenic factors from ischemic retina in order to limit neovascularization in proliferative diabetic retinopathy.[8-11]

Transpupillary thermotherapy (TTT) has been suggested as an alternative to photocoagulation. In this approach, 810-nm laser was applied with relatively low average power and very long exposures (60 seconds) over a wide spot on the retina (800 micron) producing a large heating zone. However, lack of temperature control or titration in this procedure resulted in frequent occurrences of significant retinal damage.[12]

A number of retrospective studies suggests that in 70 to 100% of CSCR patients treated with PDT using the photosensitizing drug Verteporfin is effective in reducing SRF with an improvement of retinal anatomy, visual acuity and retinal sensitivity. The therapeutic effect of PDT in CSCR is thought to result from short-term choriocapillaris hypoperfusion and long-term choroidal vascular modelling, leading to reduction in choroidal congestion, vascular hyperpermeability and extravascular leakage. But this treatment is expensive.[2,6,7]

Endpoint Management™ (EpM) is a method to precisely control and optimize the laser power and duration in order to achieve subthreshold laser treatment to the eye in order to eliminate negative consequences (scarring, vision loss) while at the same time maintaining clinical efficacy. It is thought to work by heating the chorio-retino-RPE complex above the onset of therapeutic response but below the tissue damage. It has been demonstrated that tissue response involves expression of heat shock proteins, including HSP70. Heat shock proteins act as a chaperones for refolding misfolded proteins, thereby potentially rejuvenating RPE cells and restoring their cellular function.[11,13-15] Therefore, we report the clinical outcomes of nondamaging subthreshold laser therapy with EpM for chronic CSCR, specifically evaluating changes in best-corrected visual acuity, subretinal fluid height, and metamorphopsia over a 3-month follow-up period.

Methods

This was a retrospective, non-randomized, interventional case series conducted from January 2023 to January 2024 at JEC Eye Hospitals Menteng and Kedoya in Jakarta. Chronic CSCR was defined as macular serous detachment of the neurosensory retina in which the symptoms persisted for at least 3 months and confirmed by the presence of subretinal fluid within the macula on the Optical Coherence Tomography (OCT).

Patients selection

Patients included in the study did not have any other retinal or choroidal disease that could present with similar characteristics. They also did not have previous macular laser treatment or intravitreal anti-VEGF within the last 4 months.

All subjects underwent a comprehensive ophthalmic examination, that included a thorough ocular examination using an indirect ophthalmoscope and slit-lamp examination including an autorefractometer, best-corrected visual acuity (BCVA) measurement with Snellen Chart, color fundus photography, intraocular pressure measurement, and Spectral Domain OCT (CIRRUS™ HD-OCT, Carl Zeiss Meditec, Inc).

Treatment and subthreshold endpoint management laser protocol

All patients were treated using PASCAL (Topcon Medical Laser System) Streamline at 577-nm wavelength, using 200 µm retinal spot sizes. Using EpM Software, the laser power was first titrated with 15-ms pulses and applied over the area of serous retinal detachment and adjacent non-thickened retina using 30% pulse energy with 0.25 spot spacing. The effect of the laser treatment was measured by the improvement in visual acuity, resolution of the subretinal fluid by OCT over 3 months of follow-up as primary outcomes. Secondary outcome was the absence or presence of metamorphopsia.

Statistical Analysis

Shapiro–Wilk normality testing showed that age, pre-treatment SRF, initial BCVA, and initial SRF were normally distributed, whereas duration of symptoms, post-treatment SRF, final BCVA, and final SRF were not normally distributed. Continuous variables were expressed as mean ± standard deviation for normally distributed data and median (minimum-maximum) for non-normally distributed data.

Ethics

As this was a retrospective case series with the intervention and follow up period retrieved from the medical records, the board of ethics committee deemed no ethical clearance is needed for this study.

Result

Subjects' characteristics

We included 13 eyes from 13 patients with chronic CSCR (12 males, 12 eyes; 1 female, 1 eye) at two tertiary eye hospitals (JEC Eye Hospitals Menteng and Kedoya) in Jakarta [table 1]. The median duration of CSCR was 12 (4-24) months. The mean age was 42.6 ± 10.04 years old . All subjects reported metamorphopsia as their presenting symptoms.

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Table 1. Baseline Characteristics

Variable	Value
Number of eyes	13
Male sex, n (%)	12 (92.3%)
Female sex, n (%)	1 (7.69%)
Age (years)	42.6 ± 10.04
Duration of symptoms (months)	12 (4–24)
Baseline BCVA	0.71 ± 0.29
Baseline SRF (µm)	206.9 ± 90.86
Previous anti-VEGF, n (%)	3 (23.1%)
Metamorphopsia, n (%)	13 (100%)

Laser parameters

The subthreshold laser therapies were administered using 15-ms pulses and 122.50 ± 11.65mW (power) with the average number of spots per treatment was 288 ± 95.36.

Anatomical results

Complete resolution of SRF were found in six eyes (46.13%). In those six eyes, complete SRF resolution were achieved in 12.5 (7-14) weeks. These data can be seen in Table 3. As many as twelve from thirteen eyes (92.31%) showed decrease of SRF, with mean baseline SRF value of 206.9 ± 90.86 µm and median final SRF of 16 (0-154) µm [Table 2].

Table 2. SRF Changes in All Subjects Before and After the Administration of Subthreshold Laser Therapy

Subject No	Pre-treatment SRF (µm)	Post-treatment SRF (µm)
1	161	0
2	109	0
3	214	16
4	375	22
5	298	138
6	315	0
7	224	0
8	160	42
9	254	0
10	61	45
11	250	0
12	115	74
13	154	154
Summary	206.9 ± 90.86	16 (0–154)

Clinical results

Twelve from thirteen eyes (92.31%) also demonstrated improved or stable visual outcomes. The mean BCVA significantly improved from 0.74±0.26 at baseline to median 1.0 (0.1-1.0) at the final visit. Notably, 10 eyes (76.92%) achieved final BCVA of 1.0. Individual BCVA measurements for all subjects are detailed in Table 3.

Limitations of subthreshold endpoint management laser

One subject (subject no 13) did not show any improvement in terms of anatomical (SRF reduction) as well as clinical (visual acuity) endpoints [Table 3]. One thing that stands out is the presence of subretinal fibrin in this particular eye. Subretinal fibrin may prove as poor prognostic factor in eyes with chronic CSR underwent EpM laser.

Previous treatment

Previous anti VEGF injection was proven not to be a poor prognostic factor. Three eyes in our study received prior anti VEGF injections with two eyes (66,67%) recorded improved in both SRF reduction as well as better post treatment visual acuity.

Table 3. Clinical Data from All Subjects

Subject No	Initial BCVA	Final BCVA	Initial SRF (µm)	Final SRF (µm)	Duration of complete SRF Resolution (weeks)
1	0.7	1	161	0	7
2	0.8	1	109	0	12
3	1	1	214	16	-
4	0.5	1	375	22	-
5	0.8	1	298	138	-
6	0.5	1	315	0	8
7	1	1	224	0	14
8	0.7	0.8	160	42	-
9	0.9	1	254	0	13
10	1	1	61	45	-
11	0.9	1	250	0	13
12	0.3	0.2	115	74	-
13	0.1	0.1	154	154	-
Summary	0.71 ± 0.29	1.0 (0.1-1.0)	206.9 ± 90.86	16 (0-154)	-

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Discussion

Principles of endpoint management

Photothermal therapy is based on conversion of absorbed laser light in the RPE and choroid into heat. In photocoagulation, diffusion of heat from the RPE into retina leads to thermal damage to photoreceptors or, at higher settings, even to the inner retinal cells. While destruction of a significant fraction of photoreceptors, the most metabolically active and numerous cells in the retina, is desirable to reduce metabolic load and thereby decrease secretion of angiogenic factors from ischemic retina in order to limit neovascularization.[8-11,14,15] Shorter laser exposure times have also been shown to reduce treatment discomfort during panretinal photocoagulation without compromising efficacy.[16]

EpM, however, modifies this by precisely controlling laser parameters to achieve subthreshold laser treatment to the eye in order to eliminate negative consequences (scarring, vision loss) while at the same time maintaining clinical efficacy. It is thought to work by heating the chorio-retino-RPE complex above the onset of therapeutic response but below the tissue damage. It has been demonstrated that tissue response involves expression of heat shock proteins, including HSP70. Heat shock proteins act as a chaperones for refolding misfolded proteins, thereby potentially rejuvenating RPE cells and restoring their cellular function.[11,13-15]

Endpoint management versus micropulse laser

The micropulse operating mode and terminology were described by Dorin.[17] In the traditional continuous-wave mode, a single laser pulse of 0.1–0.5 s delivers the preset laser energy. In the micropulse mode, a train of repetitive short laser pulses delivers the laser energy within an “envelope” whose width is typically 0.1–0.5s. The normal length of each pulse is 100–300 µs. The “envelope” includes “ON” time, which is the duration of each micropulse, and “OFF” time, which is the time between the micropulses. The “OFF” time is important since here the originated heat can cool down. Micropulse is not a continuous laser pulse. Each pulse train takes 200-300ms per spot. If compared to endpoint management, it less than 10 ms per spot. So it takes significantly longer for a single spot. EpM delivers faster treatment times.[12,18,19]

Micropulse does not have a clear titration protocol for producing predictable and reproducible outcomes. To replicate the therapy, certain parameters need to be consistent and documented. This might useful not only when we try to use the same protocol, but also to established optimal dose or parameters with acceptable side effects. It also lacks any visible reference so it is easy to lose track of the treatment locations. EpM can rapidly treat large areas subvisible while leaving visible markers outside the fovea region, known as landmark patterns for reference and documentation of the treatment. Markers are also important predictors that can prevent misalignment or area that were targeted by the lasers.[12,15,17,18]

Fibrin as poor prognostic factor

CSCR with fibrin deposition is a rare but severe disease that commonly causes permanent visual loss. It should be considered as a severe form of chorioretinopathy. Although most CSCRs respond to clinical treatment, including observation, conventional laser photocoagulation, and photodynamic therapy, management of CSCR with subretinal fibrin deposition remains challenging for clinicians due to its poor visual acuity and prognosis, which commonly includes retinal scarring and subretinal fibrosis.[6,20] Although conventional laser photocoagulation can be tried, but when the leak is close to the fovea, this might not be the best option. This certain condition is where subthreshold laser can be beneficial. A case report by Zhou et al showed partial resolution 3 months after subthreshold laser therapy and complete absorption in 6 months.[21] However, we experienced different results in our patient and subretinal fibrin can be considered important poor prognosis prior to the therapy in this study [Figure 1].

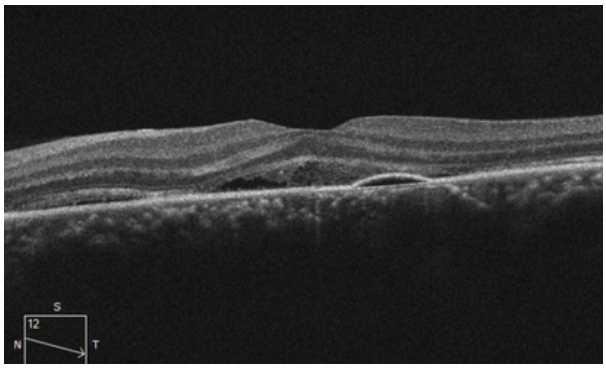

Figure 1. OCT image showing subretinal fibrin in a patient with chronic CSCR

Other EpM limitations

EpM algorithm begins with titration of the laser power to produce barely visible burns in the retina outside the arcade using 15 or 20 ms pulse duration. Laser energy corresponding to this power is then defined as 100%. So titration is the key. If laser settings are too low, the treatment will be not only subvisible but also subtherapeutic, whereas if the settings are too high, there is a danger of excessive damage to the retina, especially with the nearly con- fluent coverage close to the fovea.[11,14,15]

The only large, prospective multicentre randomised controlled treatment trial for the treatment of CSCR conducted to date is the PLACE trial.[22] This trial compared differences in percentage of patients with complete resolution of SRF, BCVA, retinal sensitivity on microperimetry, and in the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) score between CSCR patients treated with either half-dose PDT or HSML (High-density Subthreshold Micropulse). From our literature search, EpM doesn’t have any large study published yet.[1,13]

Micropulse laser treatment may be more effective in chronic CSCR eyes with focal leakage compared to eyes with diffuse leakage.[3] According to data from a PLACE trial subgroup consisting of 79 HSML- treated patients with chronic CSCR with either focal or diffuse leakage on Fundus Fluorescein Angiography (FA), 41% and 21% of patients with focal or diffuse leakage, respectively, had complete resolution of SRF at 7–8 months.[23] These findings suggests that HSML may be more effective in chronic CSCR with focal leakage on FA. Unfortunately, we did not perform FA with our patients as the contrast used is not available in our country.

Limitations of the Study

The present study is limited by its small sample size and short follow-up duration, which restrict the ability to comprehensively evaluate long-term efficacy and recurrence rates. Nevertheless, this study was designed as a pilot study and preliminary report to assess short-term anatomical and functional responses immediately following subthreshold laser therapy. In addition, the number of patients with chronic CSCR who met the strict inclusion criteria and did not receive concurrent interventions during the study period at our center was limited. Therefore, further studies with larger sample sizes, longer follow-up durations, and head-to-head comparisons with PDT are needed to better determine the effectiveness of EpM-based subthreshold laser treatment in patients with chronic CSCR.

Conclusion

Subthreshold therapy using Pascal laser with EpM in our case series appears to be associated with improvements in visual acuity and reduction or resolution of SRF in eyes with chronic CSCR. However, given the small sample size and limited follow-up duration, these findings should be interpreted with caution and do not allow for definitive conclusions regarding its long-term efficacy. This modality warrants further investigation as a therapeutic approach for chronic CSCR, as its comparative effectiveness relative to conventional laser photocoagulation and anti–vascular endothelial growth factor therapy has yet to be established. In addition, the presence of retinal fibrin at baseline may be associated with poorer outcomes following subthreshold laser therapy.

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Disclosure

The authors reported no external funding and no conflicts of interests in regards to this study.

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