Micropulse Diode Laser Treatment for Chronic Central Serous Chorioretinopathy: A Randomized Pilot Trial

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BACKGROUND AND OBJECTIVE: To evaluate 810-nm subthreshold diode micropulse (SDM) laser in patients with chronic central serous chorioretinopathy (CSC).

PATIENTS AND METHODS: Prospective, randomized, double-blind, sham-controlled pilot trial. Patients were randomized to SDM laser treatment (group 1) or sham procedure (group 2). Primary outcome measure was change in best corrected visual acuity (BCVA); secondary outcome was central macular thickness after 3 months. Laser treatment was performed along the detached area. At the 3-month visit, all patients were evaluated for re-treatment if they met re-treatment criteria.

RESULTS: Fifteen patients were included in this study: five patients in the sham group and 10 in the treatment group. At 3 months, BCVA was significantly enhanced in the treatment group ($P = .006$) compared with the sham group ($P = .498$). All patients from the sham group needed treatment after 3 months. An improvement in central macular thickness and leakage on fluorescein angiography was noted in all treated patients (in both groups).

CONCLUSION: In this limited-size, short-term exploratory study, SDM laser was effective in treating chronic CSC. There was no evidence of retinal damage induced by treatment.

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Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina and/or the retinal pigment epithelium (RPE), secondary to one or more leakage points at the RPE level. There are two main forms of disease presentation: acute CSC, most commonly seen in early adulthood, manifests as a round retinal sensory detachment lasting less than 6 months and usually has a self-limiting course, whereas chronic CSC is characterized by multifocal widespread RPE changes associated with varying degrees of leakage observed on fluorescein angiography.

The diagnosis of CSC is based on a clinical history of blurred vision and metamorphopsia with relative central scotoma, ophthalmologic examination, and fluorescein angiography. Optical coherence tomography (OCT) aids in diagnosing shallow serous detachments and is especially useful in the follow-up of affected patients. Fundus autofluorescence offers indirect information concerning the metabolic activity of the RPE and could be a noninvasive tool for monitoring RPE changes in CSC.

In most cases of acute CSC, retinal detachment resolves spontaneously within 3 months of onset. After 3 months without resolution of acute CSC or chronic CSC, continuous wave laser photocoagulation or photodynamic therapy should be considered. Direct threshold photocoagulation treatment with continuous wave laser can shorten the duration of the serous detachment, but it is not appropriate for juxtafoveal or subfoveal leakage points because it leads to retinal burn scars.

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Photodynamic therapy has been used as an alternative in the treatment of juxtafoveal and subfoveal leakage. However, it can cause adverse effects, including RPE atrophy, choroidal hypoperfusion with choriocapillaris ischemia, and choroidal neovascularization.

The classic photocoagulation treatment strategy consists of applying laser energy to obtain a confluent coagulation lesion of moderate intensity covering the leakage point. An alternate hypothesis for the photocoagulation mechanism of action suggests that its therapeutic benefits are secondary to biological activation, which does not necessarily occur in laser-necrotized tissue but in still-viable cells stimulated by sublethal thermal stress directly produced with subthreshold diode micropulse (SDM) laser exposure or indirectly caused by the equilibrating thermal wave from the laser burn.

Subvisible photocoagulation can potentially localize laser photothermal effects and decrease chorioretinal damage. SDM laser treatment using a 810-nm diode laser may limit the damage to the neural retina by raising the RPE temperature to just below the protein-denaturation threshold so that the thermal wave that reaches the neural retina is insufficient to cause either damage or a clinically visible endpoint. This therapeutic laser modality offers the possibility of minimizing iatrogenic retinal lesions. SDM delivers laser energy as a train of repetitive short diode pulses, with an “on” time and an interpulse “off” time with a sublethal cellular thermal effect. The ratio between “on” time and the total time is the duty cycle percentage, which can be adjusted to control heat intensity and spread.

This study aimed to evaluate the safety and therapeutic response of micropulse diode 810-nm laser treatment in patients with chronic CSC.

**PATIENTS AND METHODS**

This prospective, randomized, double-masked, sham-unstratified, controlled pilot exploratory trial was conducted at the Retina Service of the Federal University of São Paulo. After approval from the university’s investigational review board, 15 patients with CSC lasting more than 6 months were enrolled. Informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

The 15 patients were randomized 2:1 through double-masked random draw into two groups: 10 patients in group 1 received subthreshold 810-nm diode micropulse laser (FastPulse laser; Opto, Brazil)
treatment, and five patients in group 2 underwent sham treatment. The baseline examination included ETDRS best corrected visual acuity (BCVA), slit-lamp examination of the anterior segment, indirect ophthalmoscopy, color fundus photography using Topcon TRC-50DX (Topcon Optical, Tokyo, Japan) or Visucam (Carl Zeiss Meditec, Jena, Germany), fluorescein angiography (FA), and fundus autofluorescence using HRA-2 (Heidelberg Retina Angiograph; Heidelberg Engineering, Heidelberg, Germany). Baseline macular thickness was evaluated by spectral-domain OCT using Spectralis (Heidelberg Engineering, Heidelberg, Germany). The SD-OCT macular thickness measures included subretinal fluid if present.

The SDM laser treatment was performed over the neurosensory retinal detachment area seen at the moment of the procedure (Figure). The main outcome measure was visual acuity after 3 months, and the secondary outcome measure was change in central macular thickness. At the 3-month visit, patients from group 2 were evaluated to cross over and undergo laser treatment if they met two of the three criteria considering the main outcome measures: decreased visual acuity of at least one line from baseline, macular subretinal fluid on OCT, and significant leakage on angiography. Re-treatment was reconsidered every 3 months for all patients.

Best corrected visual acuity (EDTRS chart), color fundus photography, fundus autofluorescence, and SD-OCT were performed at 1, 3, 4, and 6 months in both groups. FA was performed at 3 and 6 months in both groups and at 9 and 12 months in patients treated in a later stage of the study. A micropulse diode laser was used for SDM photocoagulation using the Mainster standard contact lens (Ocular Instruments, Bellevue, WA). A spot size of 125 μm was used. The power was initially adjusted in the nasal retina to the minimum threshold value for a visible burn in a continuous wave mode and 300-ms duration. The device was then changed to micropulse mode with a duty cycle of 15%, and the power was increased by 1.2× threshold. The number of laser envelopes, laser power energy, SDM photocoagulation sessions, and recurrences were recorded.

Statistical analyses were performed using the Wilcoxon and Fisher tests for comparison between the two groups for continuous and categorical variables, respectively. The Wilcoxon signed-rank test was used for paired analysis of data before and after intervention. Linear regression models using generalized estimating equations (GEE) were used to evaluate longitudinal changes in visual acuity in both groups. The Kolmogorov-Smirnov normality test and Dunnett’s test for multiple comparisons were carried out to evaluate the sham-treated patients after the cross-over. A P value of less than 0.05 was considered statistically significant. The analysis was performed with Stata version 10 (StataCorp, College Station, TX) and Prism version 5 (GraphPad, San Diego, CA).

RESULTS

Fifteen eyes from 10 men and five women were divided into two groups for treatment (10 eyes) or sham (five eyes). The baseline clinical data are summarized in Table 1. The average age was 44.2 ± 5.8 years for the sham group and 39.5 ± 7.7 years for the treatment group (P = .243). The mean duration of symptoms (in months) was 31.8 ± 24.3 for the sham group and 13.3 ± 7.7 for the treatment group (P = .040). There was no statistically significant difference considering baseline central macular thickness (OCT) and visual acuity between groups. The median follow-up period was from 10.2 ± 2.7 and

<table>
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<tr>
<th>TABLE 1</th>
<th>Baseline Clinical Data of Treatment and Sham Groups</th>
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<tr>
<td></td>
<td>Sham Group</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.2 ± 5.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>45 (38-52)</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>31.8 ± 24.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>24 (12-72)</td>
</tr>
<tr>
<td>OCT central macular thickness (µm)</td>
<td>349.6 ± 61.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>324 (301-454)</td>
</tr>
<tr>
<td>BCVA (letters)</td>
<td>26.6 ± 6.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>28 (16-34)</td>
</tr>
<tr>
<td>BCVA (logMAR)</td>
<td>0.568 ± 0.135</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.54 (0.42-0.78)</td>
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OCT = optical coherence tomography; BCVA = best corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.
6.4 ± 3.2 months for the sham and treatment groups, respectively. The mean power used for the continuous wave laser to titration was 370 mW (range: 250 to 550 mW), and the mean power for the micropulse laser was 444 mW (range: 300 to 660 mW). The mean number of laser shots considering all treatments performed was 456.9 (range: 299 to 674).

On fluorescein angiography at baseline, all patients in the sham treatment group had a juxtafoveal leakage point, and three showed a posterior pole window defect, corresponding to RPE atrophy areas. In the treatment group, two patients had an extrafoveal leakage area, two had diffuse leakage with a juxtafoveal source of leakage, and six patients had a juxtafoveal leakage point. Five patients showed posterior pole window defect areas on angiography.

All five patients from the sham treatment group required treatment during the follow-up period: three patients at the 3-month visit and two at the 6-month visit. One patient treated at the 3-month visit required re-treatment at the 6-month follow-up, and one treated at the 6-month visit was re-treated at the 9-month follow-up. In the treatment group, one patient required another laser treatment at the 3-month follow-up.

Considering the first stage of the study, from baseline to 3 months of follow-up, mean best corrected visual acuity improved from 35.4 letters (20/49 Snellen equivalent) ± 11.6 at baseline to 47.9 letters (20/27 Snellen) ± 8.0 at 3 months (P = .006) in the treatment group. In the sham group, BCVA changed from 26.6 (20/73 Snellen) ± 6.8 letters at baseline to 25.6 (20/77 Snellen) ± 8.9 letters at 3 months (P = .498). Continued follow-up revealed a BCVA of 50.0 (20/25 Snellen) ± 6.8 letters at 6 months (P = .008) in the treatment group, 31.0 (20/60 Snellen) ± 8.8 letters at 6 months in the sham group (P = .225), and 39.2 (20/41 Snellen) ± 7.1 letters at 12 months (P = .042) (Table 2). Multivariate analysis showed that laser treatment led to a mean improvement of 15 letters (three ETDRS lines or double the angle of vision unit) compared with the sham group, regardless of age, gender, or duration of symptoms.

Mean central macular thickness was correlated with baseline measurements, where it ranged in the treatment group from 419.6 ± 111.8 µm at baseline to 265.4 ± 98.1 µm at 3 months (P = .091) and 247.2 ± 105.4 µm at 6 months (P = .008). In the sham group, mean central macular thickness was 349.6 ± 61.3 µm at baseline, 289.6 ± 77.7 µm at 3 months (P = .225), 283.6 ± 66.5 µm at 6 months (P = .500), and 235.8 ± 105.4 µm at 12 months (P = .008) in the treatment group, 31.0 (20/60 Snellen) ± 8.8 letters at 6 months in the sham group (P = .225), and 39.2 (20/41 Snellen) ± 7.1 letters at 12 months (P = .042) (Table 2). Multivariate analysis showed that laser treatment led to a mean improvement of 15 letters (three ETDRS lines or double the angle of vision unit) compared with the sham group, regardless of age, gender, or duration of symptoms.

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6-month follow-up in two patients, which is when treatment was initiated.

Mean BCVA improved from 27.40 ± 9.40 letters at baseline to 36.00 ± 10.07 letters at 3 months and 39.60 ± 7.37 letters at 6 months (P < .05) in the sham group (Table 4).

Mean central macular thickness ranged from 340.20 ± 45.65 µm at baseline to 252.00 ± 78.75 µm at 3 months (P < .05) and 233.60 ± 65.98 µm at 6 months (P < .01) in the sham group after the cross-over (Table 4).

No laser scars could be seen on funduscopy or on FA at the end of follow-up, as expected with the SDM technique. Two patients, one in each group, had subretinal fluid at the end of the study, but they did not present with re-treatment criteria.

**DISCUSSION**

Diode laser with micropulsed emission without a visible burn endpoint appears to reduce the risk of structural and functional retinal laser damage, allowing treatment of subfoveal lesions. It has been successfully used for diabetic macular edema and seems to be as effective as conventional argon laser with theoretical advantages.

In 2003, Bandello et al were the first to propose SDM photocoagulation for the treatment of CSC, showing positive results in a series of five cases. To date, studies on the treatment of chronic CSC have shown that SDM can provide therapeutic benefits similar to those obtained with standard-threshold continuous-wave laser photocoagulation, but without causing discernible chorioretinal lesions, allowing almost confluent therapy and re-treatment of persistent or new leaking points.

The greatest limitation of the SDM laser procedure is the difficulty of titrating the treatment without the feedback of an ophthalmoscopically visible mark. The absence of an apparent endpoint may interfere with the selective treatment, but ICG-stained RPE cells could be an option to guide the surgeon.

In the present pilot study, besides the small sample size, SDM laser treatment was first of all compared to placebo, considering the possible influence of the type A personality related to this condition. The patients were divided into two groups for the laser or sham treatment at baseline. At the 3-month follow-up, BCVA significantly improved in the treatment group (P = .006) compared with no significant visual improvement observed in the sham group (P = .498). In fact, a marked improvement in BCVA was noted in the first month in the treatment group (P = .011). There was improvement in central macular thickness on OCT and leakage on fluorescein angiography in all originally treated patients and in the patients of both groups who were treated later in the course of the study. Of 15 patients, three needed to be re-retreated without reported complications and no evidence of retinal changes on fundus indirect ophthalmoscopy examination either on fluorescein angiography or fundus autofluorescence in any patient.

Recognizing the limitations of a small sample size, a significant baseline difference was found in the duration of symptoms between the sham (31.8 ± 24.3 months) and treatment groups (13.3 ± 7.7 months), which might explain the differential effect of the diode laser or any treatment modality in this chronic condition. However, all patients in group 2 crossed over to treatment during the study follow-up, and they showed a significant improvement in visual acuity and macular thickness after laser.

In summary, this trial provides evidence that subthreshold diode micropulse laser treatment can lead to early resolution of serous retinal detachment in chronic CSC, with significant functional improvements and without leaving any sign of laser-induced lesions. The safety of SDM enables treatment closer to the fovea over extensive areas of RPE decompensation and re-treatment over the same area as needed. Further research and a large clinical trial, including direct comparison with green laser and PDT, must be performed to provide more evidence-based clinical data.

**TABLE 4**

<table>
<thead>
<tr>
<th>Chronologically Paired Mean Central Macular Thickness and BCVA of Sham Group After Cross-over</th>
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<tr>
<td>Paired Baseline</td>
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<tr>
<td>Central Macular Thickness (µm)</td>
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<tr>
<td>BCVA (letters)</td>
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*P < .05 compared to baseline.  
**P < .01 compared to baseline.  
BCVA = best corrected visual acuity.
REFERENCES