Original Article

Comparison of two protocols of subthreshold micropulse yellow laser treatment for non-resolving central serous chorioretinopathy

Abhijeet Beniwal, Nawazish Shaikh, Rohan Chawla, Shorya Vardhan Azad, Vinod Kumar, Rajpal Vohra

Purpose: To study the effect of subthreshold micropulse yellow laser treatment on central serous chorioretinopathy (CSC) and to compare two laser protocols. As per our knowledge, there are no studies comparing the two protocols of subthreshold laser. **Methods:** Twenty-three patients with non-resolving CSC of at least three months duration were treated with subthreshold laser (577 nm). Ten patients were treated with 5% duty cycle (group A) and 13 patients with 10% duty cycle (group B). At one month, best corrected visual acuity (BCVA), central macular thickness (CMT), subretinal fluid (SRF), choroidal thickness (CT) and choroidal vascularity index (CVI) were evaluated. **Results:** In group A, BCVA improved from 0.508 ± 504 to 0.174 ± 0.171 (P = 0.0058), CMT improved from 349.8 ± 168.9 micrometers (μm) to 183.3 ± 70.312 μm (P = 0.0093) and SRF reduced from 202.4 ± 158.024 to 43.8 ± 46.599 μm (P = 0.0069). In group B, BCVA improved from 0.437 ± 0.426 to 0.289 ± 0.470 (P = 0.0026), CMT improved from 280.846 ± 72.668 to 196.769 ± 72.62 μm (P = 0.0002) and SRF reduced from 110.385 ± 57.687 μm to 52.538 ± 52.111 μm (P = 0.0064). No significant difference was found in BCVA and CMT between the groups (P = 0.8716 and P = 0.8523, respectively). CSC completely resolved in 50% of cases in group A and in 69.2% of cases in group B. This difference was not statistically significant (0.423); however, the odds ratio of resolution was 2.25 times more with 10% duty cycle. No change was observed on fundus autofluorescence (FAF) following laser. **Conclusion:** Subthreshold micropulse laser can lead to resolution of SRF in 60.87% of cases (groups A and B combined). Ten per cent duty cycle had higher odds of resolution without causing any RPE damage.

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Central serous chorioretinopathy (CSC) is a disorder characterized by serous retinal detachment and/or retinal pigment epithelial (RPE) detachment with changes most often confined to the macula. It commonly affects middle-aged men with risk factors such as systemic steroid use, type A personality, smoking, hypertension and helicobacter pylori infection.[1] Focal areas of leakage are identified on fundus fluorescein angiography (FFA) as the principal source of subretinal fluid (SRF). Management of acute CSC usually consists of observation for three to six months with spontaneous resolution of SRF with good visual recovery. Spontaneous visual recovery may not always occur and recurrence may be seen in 30%–50% of cases.[2]

Intervention in CSC may be indicated in non-resolving cases as persistent pigment epithelial detachment and persistent neurosensory detachment, and recurrences affect the final visual outcome.[3] Management options besides observation include oral medications such as eplerenone and spironolactone, conventional laser therapy, photodynamic therapy and subthreshold micropulse laser (SML). Mineralocorticoid receptor antagonist such as eplerenone has been studied for its use in CSC.[4] However, at the same time, there are studies showing no benefits of eplerenone over placebo, and as such, the benefit of oral medications for CSC remains uncertain.[5] Conventional laser is employed only in patients with extra-foveal leak localized on FFA as it can cause irreversible damage to the fovea.[6] Verteporfin photodynamic therapy (PDT) is employed in acute CSC and chronic patients for resolution of fluid as well as to prevent relapses but can have side effects such as choroidal ischemia, RPE atrophy and development of choroidal neovascular membrane (CNVM).[7,8] Subthreshold micropulse laser (577 nm) has been recently introduced as an effective management strategy in patients with CSC involving the center of macula as it does not cause significant retinal damage.[9]

Multiple studies have shown the efficacy of SML in patients with CSC, but none have clearly defined the standard protocol for performing SML in patients with non-resolving CSC. Our study aimed at evaluating not only the effect of SML on non-resolving CSC but also comparing two protocols of SML such that a standard protocol may be established for its use in treatment.

Dr Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi, India

Correspondence to: Dr Rohan Chawla, RP Centre First Floor, AIIMS New Delhi - 110 029, India. E-mail: dr.rohanrpc@gmail.com

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Methods

Our study was a prospective pilot study conducted at a tertiary center in North India. The ethical clearance was obtained from the Institutional Ethics Committee and the study adhered to the tenets of the Declaration of Helsinki. All patients of age 20–50 years presenting to our outpatient department with the diagnosis of non-resolving CSC (duration >3 months) with visual acuity less than 6/9 and willing to participate in the trial were recruited. Patients were randomized using simple randomization into group A (5% duty cycle) and group B (10% duty cycle). During the study period, a total of 10 eyes were recruited in group A and 13 eyes in group B.

All patients underwent a thorough systemic and ocular examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP), and detailed anterior and posterior segment evaluation. Imaging included swept-source optical coherence tomography (SS-OCT, DRI-OCT Triton™), optical coherence tomography angiography with 4.5 × 4.5 mm sections (OCT-A, DRI-OCT Triton™), fundus short-wave autofluorescence (SpectralisHiedelberg®) fundus fluorescein and indocyanine angiography (SpectralisHiedelberg®). Choroidal thickness was measured using SS-OCT just below fovea.

SS-OCT image was analyzed using Image J software. The area of choroid was marked using free pencil tool from RPE–Bruch's membrane complex to sclero-choroidal junction. The image was converted into 8 bit and binarized using Niblack's auto local threshold tool. Its histogram was then evaluated. The black pixels were taken to represent the luminal area. Total number of black pixels divided by total number of pixels in the cropped choroidal section gave the choroidal vascularity index[10] [Fig. 1].

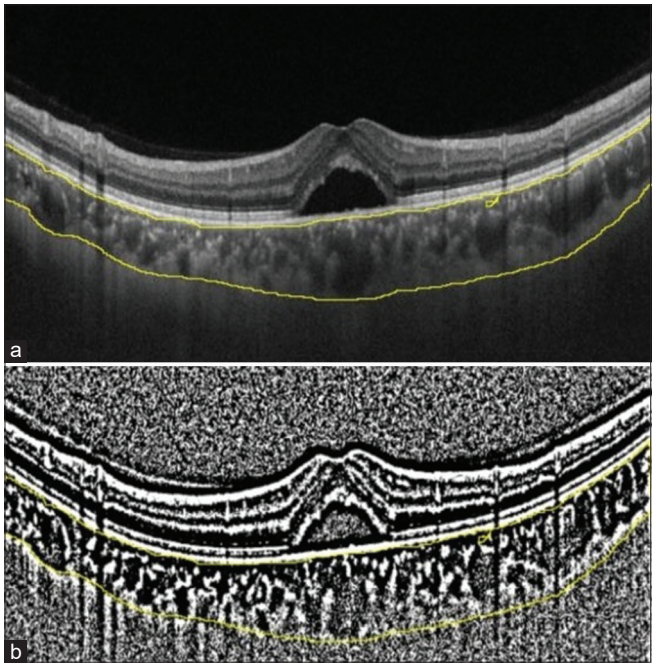

Figure 1: (a) SS-OCT image with choroid ma rked from RPE–Bruch's complex to sclero-choroidal junction (between yellow lines) using freehand tool on Image J software. (b) Same image converted to 8 bit and binarized using Niblack's auto local threshold tool of Image J software

Ten eyes in group A and 13 eyes in group B underwent SML using the LightMedTruScan™ with yellow laser 577 nm. Titration of energy was done by placing a barely visible laser spot of size 100 microns with 50 msec exposure (visible within 3 sec of application) near the arcade, following which the duty cycle was reduced to 5% for group A and 10% for group B. A square grid of four such spots was chosen and at least four to five successive spots were given at rapid intervals at the site of leakage localized on FFA. The fluorescein leak was targeted with the laser. A pattern laser spot in the form of four dots with spot size of 50 microns was used. This was done to ensure proper coverage of the area of leak as sometimes a single spot of 50 microns may miss the exact leaking spot.

Follow-up was done at one month after SML. At one month, BCVA, central macular thickness (CMT), subretinal fluid (SRF), choroidal thickness (CT), choroidal vascularity index (CVI) and FAF images were evaluated.

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) and Stata version 12.1, and data were expressed as mean and standard deviation (SD). Groups were compared using analysis of variance (ANOVA) and the *P* value was considered significant if < 0.05 and highly significant if < 0.001. The relationship between continuous variables and the comparison groups was assessed through either *t*-tests, if the continuous variables were normal, or through non-parametric Wilcoxon tests, if the continuous variables were non-normal.

Results

A total of 23 eyes of 23 patients with diagnosis of non-resolving CSC were recruited and treated with subthreshold micropulse yellow laser. Five patients were female and 18 patients were male. Patients were followed up for one month. Mean age was 40.3 years overa ll: 41.3 years in group A and 39.6 years in group B. Groups were comparable to each other with respect to vision, CMT and height of SRF prior to treatment and post treatment ($P > 0.05$) [Table 1].

BCVA improved from 0.508 ± 0.504 to 0.174 ± 0.171 logMAR scale in group A ($P = 0.0058$) and 0.437 ± 0.426 to 0.289 ± 0.470 in group B in logMAR scale ($P = 0.0026$). In group A, CMT was 349.8 ± 168.669 μm prior to treatment and 188.1 ± 76.788 μm post treatment ($P = 0.0093$). In group B, CMT was 280.846 ± 72.668 μm prior to treatment and 199.154 ± 75.259 μm post treatment ($P = 0.0015$). In group A, height of SRF reduced from 202.4 ± 158.024 μm to 52.3 ± 57.529 μm ($P = 0.0069$). In group B, height of SRF reduced from 110.385 ± 57.687 μm to 45.769 ± 49.078 μm post treatment ($P = 0.0026$) [Figs. 2 and 3].

There was no statistically significant change in the sub-foveal choroidal thickness in group A before and after laser treatment (429.2 ± 120.815 vs 426.8 ± 128.42 μm, $P = 0.9331$). Similarly, in group B, the change in choroidal thickness from 497.539 ± 102.274 to 463.462 ± 80.012 μm ($P = 0.0959$) was not statistically significant. In our study, the CVI also did not show any significant change post treatment in either group (In group A, CVI changed from 0.642 ± 0.013 to 0.644 ± 0.016 [$P = 0.4534$]; in group B, CVI changed from 0.6378 ± 0.0116 to 0.6381 ± 0.0122 [$P = 0.9431$]).

In group A, CSC in 5 out of 10 patients resolved. In group B, CSC in 9 out of 13 patients resolved. Odds of resolution was

Table 1: Table of baseline characteristics of two groups and brief statistical analysis showing that the two groups were comparable

	s no	age	gender (male-1, female 2)	laterality (right eye-1, left eye-2)	location of leaks in relation of fovea- sub-0, juxta-1, extra 2	Maximum height of serous retinal detachment	Sub foveal choroidal thickness	vision 0 in logmar	cmt 0
Group 1	1	29	1	2	1	315	471	0.3	482
	2	36	1	1	0	77	608	0.48	248
	3	42	1	1	2	145	323	0.48	270
	4	50	1	2	1	57	300	0.3	192
	5	42	1	1	1	169	233	0.48	264
	6	45	2	2	2	180	400	0.18	415
	7	48	2	2	0	208	550	0.18	310
	8	39	1	1	1	214	548	0.48	403
	9	41	1	2	1	67	458	0.3	176
	10	41	2	2	2	592	401	1.9	738
Group 2	1	41	1	1	1	80	328	0.48	235
	2	36	1	1	2	23	476	0.48	212
	3	34	2	1	1	128	560	0.18	352
	4	41	1	1	1	100	363	0.18	297
	5	35	1	1	2	79	511	0.48	220
	6	30	1	1	2	111	575	0.48	214
	7	30	1	2	2	95	719	0.18	249
	8	36	1	2	1	103	561	0.18	264
	9	45	1	2	1	70	511	0.3	180
	10	50	2	2	1	97	440	0.18	345
	11	42	1	2	0	108	440	0.48	388
	12	45	1	1	1	263	556	0.3	407
	13	50	1	1	1	178	428	1.78	288

Best corrected visual acuity before treatment in both groups was compared. In group A mean visual acuity in log mar scale was 0.508 ± 0.504. In group B it was 0.437±0.426. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was applied and probability value was 0.5570. Both groups were comparable. Central macular thickness was 349.8±168.669 micrometre in group A pre-treatment. It was 280.846 ± 72.668 in group B pre-treatment. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was applied and probability was 0.3684 which was not significant and two groups were comparable. Height of subretinal fluid in group A was 202.4±158.024 micrometre pre-treatment. It was 110.385 ± 57.687 micrometre in group B pre-treatment. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was applied and probability was 0.1538 and both groups were comparable. In group A sub foveal choroidal thickness was 429.2±120.815 micrometre pre-treatment. In group B it was 497.539 ± 102.274 micrometre. Two-sample t test was applied and probability was 0.1567 and both groups were comparable

2.25 times higher with 10% duty cycle when compared to 5% [Figs. 2 and 3].

Post laser treatment, no patient had any appreciable RPE changes on FAF. All patients received single cycle of subthreshold laser as per the above-described protocol.

Discussion

Subthreshold micropulse laser treatment is effectively used for leaks involving the fovea as it has less or no significant RPE damage. In micropulse photocoagulation, laser energy is dispended in a burst or as an envelope of micropulses. This limits the time taken for heat conduction to raise the temperature in the adjacent tissue, thereby significantly reducing collateral damage. Repetitive micropulses summate to produce the desirable therapeutic effects with milder retinal irradiances with lower temperature rise, and hence is safe for use at the fovea. Multiple and overlapping spots with no visible clinical endpoint are delivered to the areas of diseased RPE with the aim of inducing a biological response that promotes the recovery and restoration of the outer blood–retinal barrier and ultimately, the resorption of the subretinal fluid.[11]

Clinical efficacy of SML in non-resolving CSC has been shown by multiple studies, but each one uses its own protocol for the subthreshold laser with no standard protocol of treatment. Some studies adjust laser power upward to the minimum threshold value for a visible burn in a continuous wave mode and then switch to micropulse mode. Other researchers have also used the micropulse mode for power titration and applied 50%–80% of the minimum threshold power to cause a barely visible burn.[12] The former method was used in our study with the duty cycle being then reduced to 5% for group A and 10% for group B. The power in our study varied from 80 to 240 MW for both the groups with an average of 143 MW in group A and 147.69 MW in group B.

Several studies have been done on subthreshold laser treatment, but exact duty cycle has not been agreed upon. Too less a power could be sub-therapeutic, whereas too high a power can cause retinal damage. Elhamid *et al*.,[13] in their prospective interventional study, showed the safety and efficacy

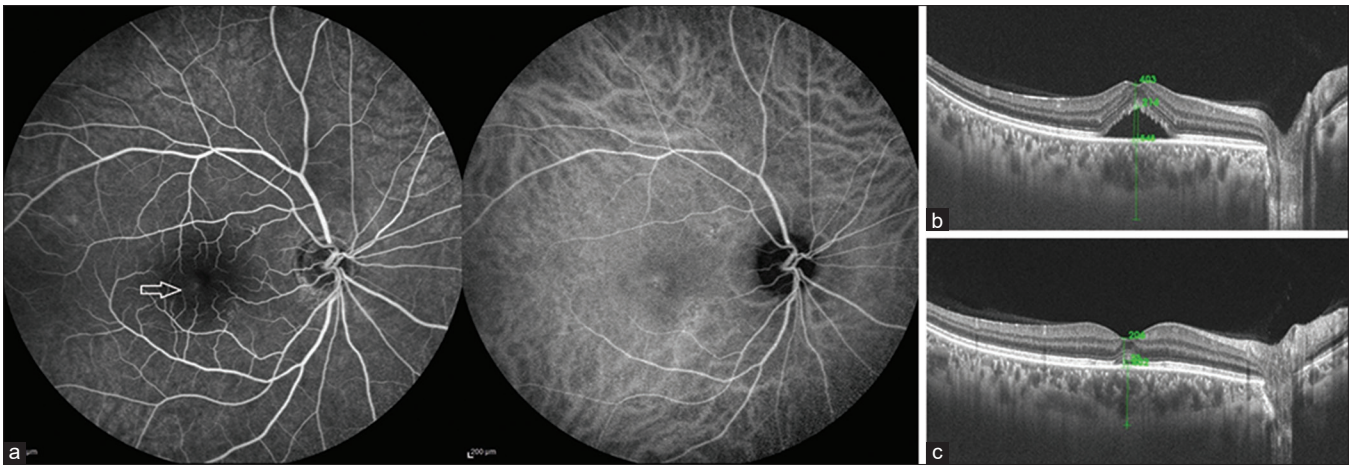

Figure 2: (a) Fluorescein and indocyanine green angiography image of a patient of group A showing leak (arrow). (b) Pre-treatment SS-OCT image. Central macular thickness, subretinal fluid height and choroidal thickness beneath fovea have been measured. (c) Post-treatment SS-OCT image showing resolution of CSC. The central macular thickness and choroidal thickness beneath the fovea have been measured

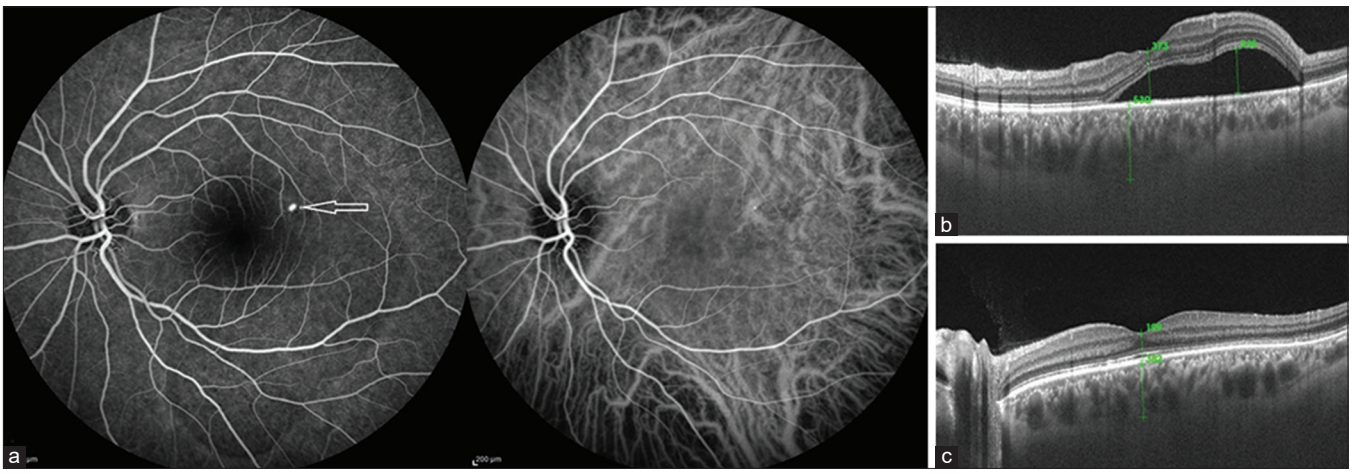

Figure 3: (a) Fluorescein and indocyanine green angiography image of a patient of group B showing leak (arrow). (b) Pre-treatment SS-OCT image. Central macular thickness, subretinal fluid height and choroidal thickness beneath the fovea have been measured. (c) Post-treatment SS-OCT image showing resolution of CSC. The central macular thickness and choroidal thickness beneath fovea have been measured

of SML using a 10% duty cycle in patients with non-resolving CSC. Yadav *et al*.,[9] in their retrospective analysis, showed improvement in visual acuity after 577 nm subthreshold laser using a 10% duty cycle which was found to be safe. Similarly, other studies have shown the efficacy and safety of 577 nm SML with 10% duty cycle.[14] Arsan *et al*.,[15] in their prospective study, showed the efficacy of 577 nm SML with 5% duty cycle and showed 82.0% resolution of SRF at three months with no RPE damage. Similarly, Işık *et al*.[16] used 5% duty cycle in their retrospective study with improvement in BCVA in all patients, with resolution of SRF in 67.2%. The present study not only mirrored the results of other studies showing clinical improvement in visual acuity after subthreshold laser, but also highlighted a standard protocol for subthreshold laser in patients with CSC. In our study, 577 nm sub-threshold laser was used in patients with CSC, with a duty cycle of 10% and 5%. There was an overall resolution of SRF seen in 60.87% of cases with absence of RPE damage in 100% of patients. Ten per cent duty cycle not only reduced SRF, but also improved visual acuity and did not result in any visible RPE damage, as shown by post-laser FAF. Odds ratio of the two groups were compared, and the group treated with duty cycle of 10% had a higher odds ratio of 2.25 of resolution as compared to the group with 5% duty cycle.

In our study, the choroidal parameters such as choroidal thickness and CVI did not show any statistically significant change post laser treatment. Previous studies on choroidal parameters have documented conflicting results. In a study by Işık *et al*.[16] the initial median sub-foveal choroidal thickness value before treatment was significantly higher than the values of the third month's visit ($P < 0.001$). Similarly, in a study by Arsan *et al*.,[15] initial median sub-foveal choroidal thickness was recorded as 364 µm and subsequently 342 µm at final follow-up ($P < 0.001$). On the other hand, Ho *et al*.[17] investigated the choroidal thickness following photodynamic therapy (PDT) and subthreshold laser. Choroidal volume did not show significant change after subthreshold laser treatment, but it reduced significantly after PDT. Likewise, Van Rijssen *et al*.[18] assessed the effect of PDT and high-density subthreshold micropulse laser (HSML) on CVI. They did not find any significant change in CVI in either group.

In our series, a total of 3 patients, 2 in group A and 1 in group B, had sub-foveal leaks while the other cases had juxta-foveal leaks. Sub is 0 microns from fovea. Juxta is up to 200 microns from the center of the fovea and beyond 200 microns was taken as extrafoveal. Subthreshold laser was found safe for both sub-foveal and juxta-foveal leaks, and no case showed a drop in visual acuity or any visible alteration of FAF.

The drawback of our study is its small sample size. A larger prospective study using the 10% duty cycle with the treatment protocol standardized in this study would be better able to determine the efficacy of this therapy.

Conclusion

Subthreshold micropulse laser is an effective treatment in cases of central serous chorioretinopathy. It led to resolution of subretinal fluid in 60.87% cases in our study. Significant improvement in visual acuity was seen following resolution of subretinal fluid. There were no undesirable effects of subthreshold laser including RPE changes. No changes were visible clinically or on FAF in the retinal pigment epithelium following subthreshold laser.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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