

Multifocal electroretinography-assisted anatomical and functional evaluation of subthreshold green laser in acute central serous chorioretinopathy

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Purpose: To compare observation versus subthreshold green laser (STL) in acute central serous chorioretinopathy (CSC) in terms of anatomical and functional outcomes. **Methods:** Prospective randomized interventional study. 30 eyes with the first episode of acute CSC underwent complete ophthalmologic examination, measurement of best-corrected Snellen visual acuity (BCVA), contrast sensitivity (CS), fundus fluorescein angiography (FFA), spectral-domain optical coherence tomography (SD-OCT), and multifocal electroretinography (mfERG) at baseline. Patients were randomized equally to group A (observation) or group B (STL using 532 nm wavelength applied to the leakage point). Outcome measures included BCVA, CS, central foveal thickness (CFT), and mean macular thickness (MMT) on SD-OCT and P1 amplitude and implicit time (IT) on mfERG. Patients were followed up for 6 months. **Results:** Mean BCVA was comparable between the two groups on follow up; however, mean CS was significantly higher in group B at 6 months ($P = 0.032$). CFT was significantly lower in group B at 1 month ($P = 0.001$) and 3 months ($P = 0.049$); however, this difference was not maintained at 6 months ($P = 0.265$). P1 amplitude and IT in all 5 rings were comparable between the two groups at baseline. On follow up, P1 amplitude of ring 1 became significantly higher in group B at 3 months ($P = 0.036$) and 6 months ($P = 0.022$). **Conclusion:** Immediate treatment of acute CSC with STL, as compared to conservative management, leads to more rapid resolution on SD-OCT and superior functional outcomes as evidenced by CS and mfERG.

Key words: Acute central serous chorioretinopathy, contrast sensitivity, multifocal electroretinography, spectral-domain optical coherence tomography, subthreshold laser

Central serous chorioretinopathy (CSC) is an idiopathic disorder encountered in young or middle-aged adults with a male preponderance. It presents as a localised detachment of the neurosensory retina and/or retinal pigment epithelium (RPE), frequently involving the posterior pole. Type A personality, stress, smoking, pregnancy, and steroid use are the common risk factors.^[1] CSC is currently classified within the pachychoroid disease spectrum owing to choroidal vascular hyperpermeability and congestion, which leads to the impaired barrier function of the RPE with one or more leakage sites at the level of the RPE.^[2]

CSC includes two distinct entities classically described as acute and chronic based on the duration of neurosensory detachment (NSD) and the presence of RPE alterations. Acute CSC presents with blurred vision, central scotoma, metamorphopsia, micropsia, dyschromatopsia, and/or reduced contrast sensitivity (CS). The condition usually runs a benign course with spontaneous resolution of the NSD within 1 to 3 months.^[1] Hence, observation is the current standard of care.^[3] However, subretinal fluid (SRF) accumulation in acute CSC causes damage to the photoreceptors which may persist even once the fluid is reabsorbed and manifest as diminished CS and scotomas despite recovering normal visual acuity.^[4]

In addition, 30%–50% cases of acute CSC recur and 5%–10% progress to the phase of chronic CSC which is the more severe form characterized by exacerbations and remissions, persistent NSD, PED, RPE atrophy, pigmentary changes and carries a more serious long-term visual prognosis.^[1] Therefore, it is imperative to explore treatment options for acute CSC with special emphasis on safety and lack of side effects.

The efficacy of threshold laser photocoagulation and photodynamic therapy (PDT) has been demonstrated in CSC.^[5] However, collateral damage invariably accompanies the former due to the pre-requisite of producing a visible burn. Subthreshold laser (STL) produces similar therapeutic effect as threshold laser with no collateral damage discernable by limiting the thermionic effect to the RPE and is a promising non-destructive treatment option in all types of leaks in CSC.^[6] This can be achieved by decreasing the laser exposure duration and using a nonvisible clinical end point. Stimulation and enhancement of the healing response of the RPE by STL improve its pumping and barrier action, facilitating resorption of SRF in CSC.^[7]

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Conventional investigative modalities such as optical coherence tomography (OCT), fundus fluorescein angiography (FFA), and fundus autofluorescence (FAF) are irreplaceable for the diagnosis and management of acute CSC. However, they provide largely anatomic information. The visual function can be assessed psychophysically by CS, color contrast, and dark adaptation and objectively by multifocal electroretinography (mfERG). mfERG developed by Sutter and Tran provides topographic evaluation of the macular function noninvasively through simultaneous measurements of multiple retinal responses at different locations.^[8] Previous studies have demonstrated that first order mfERG response amplitudes at the central macula are significantly reduced in CSC with sparing of the more peripheral retina.^[9]

The purpose of this study is to evaluate STL as a treatment modality in acute CSC in terms of functional parameters (BCVA, CS, and mfERG) in addition to anatomic parameters [on spectral domain OCT (SD-OCT)] and to compare it with the current standard of care, i.e., observation.

Methods

This was a prospective randomized interventional study on observation versus STL in acute CSC conducted at a tertiary eye center. Institutional ethical clearance was obtained prior to the commencement of the study. The study was performed in accordance with the tenets of the declaration of Helsinki. Informed consent was obtained from all patients at the outset.

Patients aged ≥ 18 years, willing and able to provide informed consent, with CSC of less than one month duration, best-corrected Snellen visual acuity (BCVA) better than 6/60, and SRF involving the fovea on SD-OCT were included. Patients with any significant media opacity precluding clinical and other examination, chronic CSC or recurrent CSC, leakage point within 350 μm of the foveal center or multifocal leaks, history of any previous retinal intervention like retinal laser, intravitreal injection or surgery, cataract extraction or any other intraocular surgery within the last 3 months, and YAG capsulotomy within 1 month or subjects with any other ocular diseases were excluded from the study.

Detailed demographic data including age, sex, duration of symptoms, history of pregnancy, steroid use, and/or smoking were noted. All patients underwent recording of BCVA (Snellen chart, converted to logMAR units for statistical analysis),^[10] CS (Pelli–Robson chart, converted to logMAR units for statistical analysis),^[11] slit-lamp biomicroscopy, FFA (Topcon TRC 50 DX, Oakland, NJ), and SD-OCT (RTVue, Optovue, San Francisco, CA) at baseline. Measurement of BCVA, CS, slit-lamp biomicroscopy, and SD-OCT were repeated at 1, 3, and 6 months follow-up. Parameters analyzed on SD-OCT were central foveal thickness (CFT) and mean macular thickness (MMT). MMT was calculated as the average of all 9 locations on the macula (5 mm). Patients who developed a recurrence of CSC at any visit or who had persistent CSC till 6-month follow-up were excluded from the study.

The first-order kernel mfERG responses were recorded using RETI Port/Scan 21 (Roland Consult, Germany) and DTL electrodes under pharmacologic dilatation, according to ISCEV guidelines^[12] at baseline and at 3 and 6 months follow-up. The 61-scaled hexagon-based pattern stimulus was used.

Individual mfERG responses for the hexagons were grouped into 5 concentric rings centered on the fovea for analysis (2° , $2\text{--}5^\circ$, $5\text{--}10^\circ$, $10\text{--}15^\circ$, and $>15^\circ$). The amplitudes and implicit times (IT) of the P1 wave were evaluated. P1 amplitude was measured from the N1 trough to the P1 peak and expressed as response amplitude per unit area (nV/deg^2). IT of P1 wave was measured from the time of presenting the stimuli and expressed as milliseconds (ms).

Eligible eyes were randomly assigned to observation (group A) or STL (group B) using a centralized computer-generated randomization list. STL treatment was performed as an outpatient procedure under topical anesthesia and mydriasis. A slit-lamp integrated frequency-doubled Nd:YAG Photocoagulator (Zeiss VISULAS 532 s) using 532-nm wavelength was used with “Ocular” mainster (standard) focal/grid contact lens applied to the cornea with methylcellulose fluid. A test spot was applied to the retina nasal to the optic disc using 100 μm spot size and 200 ms duration, and the power was increased to produce a mild gray lesion (visible burn) at the level of the outer retina. The energy needed for the visible burn was kept constant but the duration was halved to 100 ms and treatment was carried out. The laser was applied to the leakage site with immediate cessation on the occurrence of subtle RPE color changes. Post treatment, patient was prescribed a topical antibiotic (ciprofloxacin 0.3%) for 3 days and followed up as per protocol.

Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, IBM Corporation) Statistical software version 21.0. Statistical significance was determined by Chi-square/Fisher’s exact test for qualitative variables. Quantitative variables were compared using independent t-test/Mann Whitney test (for nonparametric data) between the two groups. A *P* value less than 0.05 was considered statistically significant.

Results

30 eyes of 30 patients with the first episode of acute CSC less than one month in duration and with a single angiographic leak were recruited, with 15 eyes in each group. All patients were of Indian origin. The ages of the patients ranged from 27 to 62 years with a mean of 40.8 ± 10.61 years in group A and from 18 to 62 years with a mean of 39 ± 9.52 years in group B. There was one female in group A and 3 in group B and rest were all males. The mean duration of symptoms was 14.47 ± 10.41 days in group A and 14.13 ± 9.83 days in group B. In both groups, one patient each was a smoker, who were counseled to discontinue smoking. None of the patients had history of steroid intake in any form or pregnancy. There were no significant differences between the 2 groups with regards to baseline demographic data [Table 1].

Table 1: Baseline characteristics of the 30 eyes in the study

	Group A (n=15)	Group B (n=15)	P ¹
Age, years	40.8±10.61	39±9.52	0.917
Gender, Male	14	12	0.598
Female	1	3	0.598
Duration of symptoms, days	14.47±10.41	14.13±9.83	0.967

Values are Mean±Standard Deviation. ¹ Mann-Whitney test

Mean BCVA in the two groups was matched at baseline and remained comparable between the two groups at 1, 3, and 6 months follow-up. Mean CS did not differ significantly between the two groups at presentation and at 1 and 3 months follow-up. However, at 6 months, mean CS was significantly higher in group B [Table 2]. Slit-lamp biomicroscopy showed subfoveal NSD in all eyes, which was confirmed on SD-OCT. FFA performed in all eyes localized the point of leak. Mean CFT and MMT on SD-OCT were comparable in both groups at baseline. Mean CFT was significantly lower in group B following STL at 1 and 3 months follow-up and mean MMT was significantly lower in group B at post STL at 1 month; however, this difference was not maintained at the final follow-up of 6 months [Table 2].

The comparisons of the mean P1 amplitudes and IT in all 5 rings between the two groups at presentation and at 3 and 6 months follow-up are detailed in Table 3. Mean P1 amplitudes and IT in all the rings were comparable between group A and B at baseline. At 3 and 6 months follow-up, mean P1 amplitudes in ring 1 were significantly higher in group B, while the mean P1 IT in all 5 rings did not differ significantly between the groups. Representative cases of both groups with sequential mfERG responses are depicted in Figs. 1 and 2.

Discussion

Acute CSC typically has a benign, self-limiting and majority of the physicians prefer to observe the patient with an acute, first time episode for at least 3 months before suggesting any

Table 2: Comparison between BCVA, CS, CFT, and MMT on SD-OCT between groups A and B at baseline and follow up

	Group A (n=15)	Group B (n=15)	P-value ¹
BCVA, logMAR units			
Baseline	0.41±0.3	0.44±0.37	0.946
1 month	0.14±0.14	0.14±0.17	0.841
3 months	0.11±0.13	0.03±0.09	0.057
6 months	0.05±0.08	0.02±0.08	0.189
CS, logMAR units			
Baseline	1.09±0.49	1.03±0.45	0.4
1 month	1.33±0.14	1.4±0.11	0.145
3 months	1.43±0.11	1.48±0.05	0.169
6 months	1.42±0.14	1.49±0.04	0.032
CFT, microns			
Baseline	634±199.33	514.47±140.36	0.068
1 month	305.2±80.54	231.93±38.16	0.001
3 months	265.67±76.69	221.67±24.29	0.049
6 months	226.2±32.77	237.8±22.11	0.265
MMT, microns			
Baseline	496.04±142.59	426.53±95	0.127
1 month	316.24±58.17	274.51±16.48	0.007
3 months	294.73±41.11	280.18±12.33	0.663
6 months	274.29±17	279.74±12.86	0.330

Values are Mean±Standard Deviation. ¹ Mann-Whitney test

Table 3: Comparison between P1 amplitude (nV/deg²) and P1 implicit time (IT, milliseconds) on mfERG between groups A and B at baseline and follow up

	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
P1 amplitude (baseline)					
Group A (n=15)	53.49±22.04	37.5±13.1	29.4±9.13	20.68±6.02	16.8±5.44
Group B (n=15)	56.14±27.05	40.82±16.48	29.6±8.61	19.49±5.07	16.28±4.59
P-value ¹	0.959	0.789	0.998	0.821	0.954
P1 amplitude (3 months)					
Group A (n=15)	73.23±18.64	41.76±13.24	26.46±8.76	17.81±5.52	15.16±5.51
Group B (n=15)	94.39±27.11	45.72±12.21	27.51±7.77	17.94±5.25	15.21±4.48
P-value ¹	0.036	0.402	0.731	0.948	0.982
P1 amplitude (6 months)					
Group A (n=15)	67.46±24.14	37.82±10.05	26.41±6.1	17.55±4.11	14.98±3.89
Group B (n=15)	87.36±20.72	45.21±11.27	28.64±8.55	18.2±5.09	14.75±4.34
P-value ¹	0.022	0.068	0.418	0.702	0.880
P1 IT (baseline)					
Group A (n=15)	48.21±2.28	45.45±2.1	43.93±2.2	43.54±1.76	43.86±1.51
Group B (n=15)	46.64±6.65	44.86±3.76	43.67±2.67	44.07±1.39	44.07±1.48
P-value ¹	0.948	0.812	0.833	0.799	0.966
P1 IT (3 months)					
Group A (n=15)	47.41±2.71	43.54±2.78	42.94±1.95	42.81±2.51	43.15±2.12
Group B (n=15)	46.75±1.78	43.61±2.13	43.28±2.16	43.49±2.1	43.68±1.89
P-value ¹	0.438	0.936	0.654	0.433	0.365
P1 IT (6 months)					
Group A (n=15)	47.08±2.37	43.67±1.97	43.03±1.94	43.42±1.17	43.69±1.22
Group B (n=15)	46.47±1.52	42.89±1.93	43.35±1.37	43.42±1.28	43.55±1.41
P-value ¹	0.467	0.119	0.656	1.000	0.746

Values are Mean±Standard Deviation. ¹ Mann-Whitney test

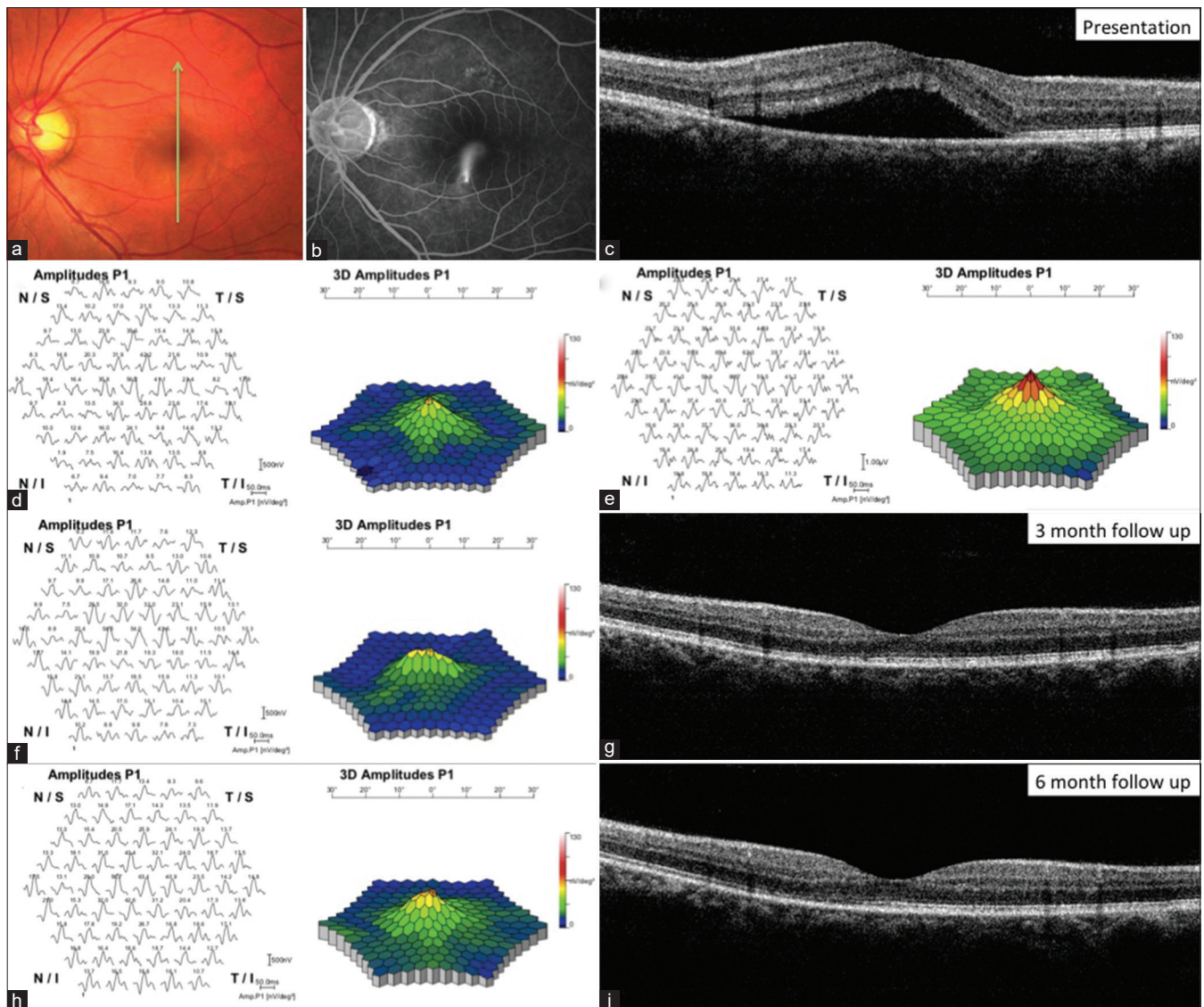


Figure 1: Group A, patient 14 (a) Color fundus photograph of the left eye of a 32-year-old male with acute CSC of 4 days duration. BCVA was 0.18 and CS was 1.35. (b) FFA showed typical smoke stack leak inferior to fovea. (c) Vertical SD-OCT scan depicted a subfoveal neurosensory detachment (NSD). (d) mfERG demonstrated reduced P1 amplitude in the central elements with preserved peripheral responses. (e) mfERG response from a age and sex matched control displaying normal results for comparison. (f and h) Sequential mfERG responses at 3 and 6 months following conservative management displayed improvement in the P1 amplitudes. (g and i) Vertical SD-OCT scans at 3 and 6 months follow-up showing resolution of the NSD. BCVA remained stable at 0 and CS was 1.5 at both visits

mode of treatment.^[3] Unfavorable visual prognosis has been attributed to recurrent attacks or less frequently to conversion to chronic course of the disease which may result in permanent impairment of visual acuity.^[1] Following spontaneous resolution, the final result depends on the eventual damage inflicted on foveal photoreceptors by SRF accumulation in the acute phase.^[13] Even after CSC resolution and recovery of normal visual acuity, patients may continue to complain about metamorphopsia, scotomas, dyschromatopsia, or reduced CS.^[4] Thus, early intervention to accelerate SRF resolution by a safe yet effective therapeutic modality is required.

Threshold laser treatment of the RPE leak is a therapeutic option for extrafoveal leaks in CSC. While data in acute CSC is limited, improved vision and CS following laser photocoagulation have been reported.^[14] However, the

established end point of a visible leak inevitably results in collateral damage which may manifest as reduced CS, abnormal color vision, and scotomas. The laser scars may progressively enlarge and predispose to chorioidal neovascularization (CNV).^[5] PDT is the modality of choice for juxtafoveal and subfoveal leaks but it can also result in RPE atrophy, choriocapillaris ischemia, and transient central scotomas.^[15] Cost and availability are additional issues with PDT. Hence, it is reserved for chronic CSC and limited data is available on the clinical utility of PDT in acute CSC.^[16] STL has been postulated to stimulate and enhance the healing response of the RPE, thus improving its pumping and barrier action and successful treatment of acute CSC has been reported with its use.^[6,17,18] Our study demonstrated that compared to observation, STL leads to significantly faster resolution on

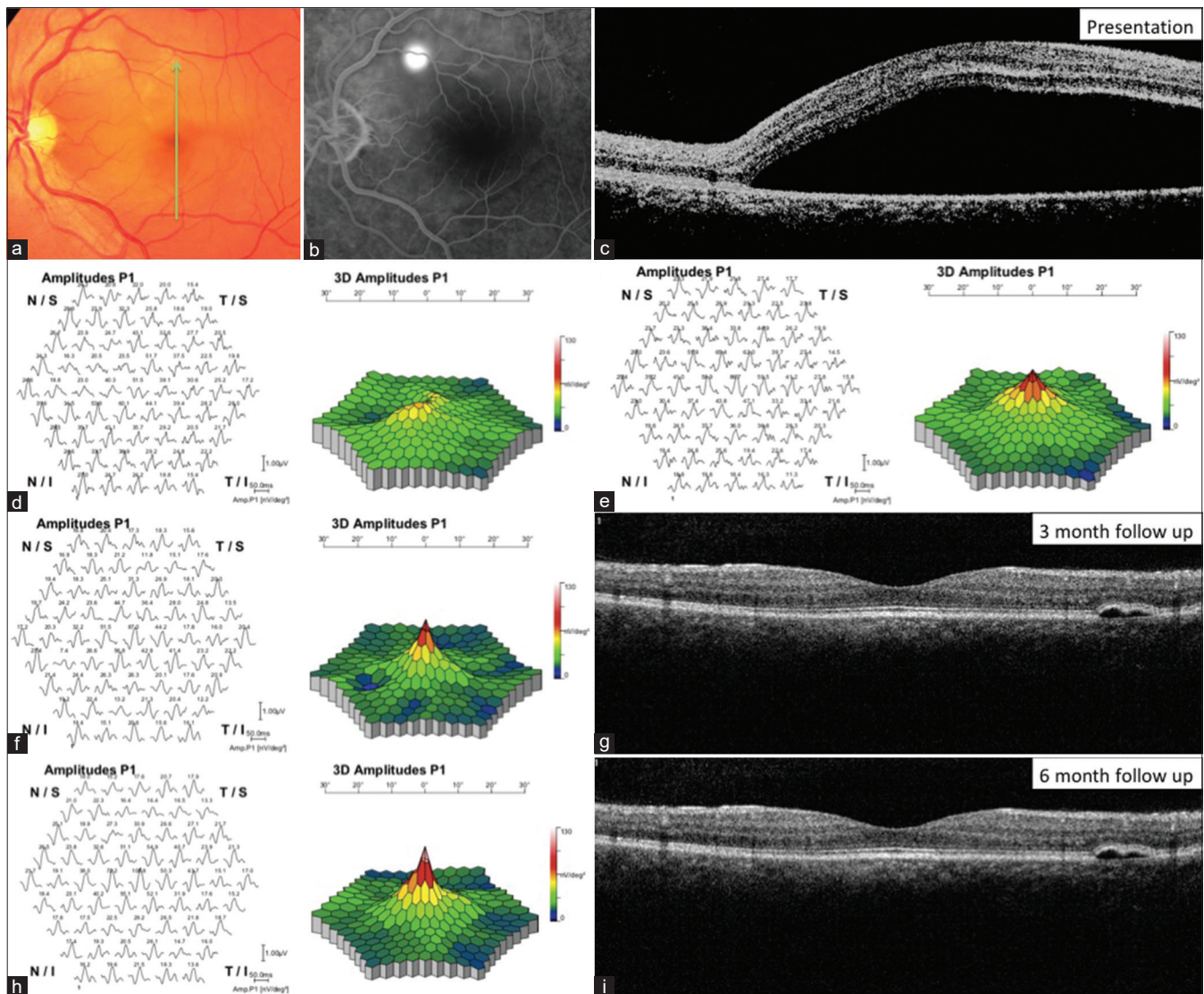


Figure 2: Group B, patient 8 (a) Color fundus photograph of the left eye of a 35-year-old male with acute CSC of 15 days duration. BCVA was 0.6 and CS was 0. (b) FFA revealed an ink blot leak superior to fovea. (c) Vertical SD-OCT scan showed a subfoveal neurosensory detachment (NSD). (d) mfERG demonstrated decreased P1 amplitude in the central elements with preserved peripheral responses. (e) mfERG response from a age and sex matched control displaying normal results for comparison. (f and h) Sequential mfERG responses at 3 and 6 months following STL depicting increase in the central responses. (g and i) Vertical SD-OCT scans at 3 and 6 months follow up showing resolution of the NSD with some RPE irregularity inferiorly. BCVA increased to 0.18 and 0 while CS remained 1.5 at both visits

SD-OCT at 1 and 3 months follow-up as seen by reduction in CFT, though the difference is not maintained at 6 months follow-up.

Diminished CS is a common sequela following spontaneous resolution of acute CSC with no known effective treatment.^[4] Our study showed that while BCVA was comparable between the observation and STL groups, CS at the final follow-up of 6 months was significantly better in the patients who received STL. This could be attributed to accelerated resolution of SRF following STL which in turns limits the photoreceptor damage. This is similar to the results obtained by Behnia *et al.*;^[6] however, they employed a different mode of STL where treatment was applied to the entire area of serous detachment. Arora *et al.*^[17] demonstrated that both BCVA and CS were significantly better and recurrences or persistence of CSC was significantly lesser when patients with acute

CSC are treated with subthreshold diode micropulse laser. In contrast to this, Ambiya *et al.*^[19] concluded that early focal laser photocoagulation using yellow laser was not superior to sham laser in acute CSC in terms of BCVA, low contrast BCVA, CMT, and height of NSD on SD-OCT and retinal sensitivity on microperimetry.

mfERG reflects the bioelectric activity of preganglionic retinal elements such as photoreceptors and bipolar cells and has been shown to be useful for the objective functional assessment of the macula in patients with CSC.^[20] Subnormal mfERG amplitudes and latencies have been shown to persist after spontaneous resolution of CSC and P1 latency negatively correlates with BCVA.^[21] The cellular generators of the P1 component of MF-ERG are predominantly ON and OFF bipolar cells, i.e., the inner retinal layers;^[22] this suggests impairment in the conduction of electrical responses from these retinal layers.

This is the first report that prospectively compared macular function using mfERG between eyes that were observed and those that underwent STL treatment in acute CSC. To the best of our knowledge and literature search, mfERG changes following STL in acute CSC have not been elaborated earlier. Our results demonstrated that P1 amplitude in ring 1 was significantly higher after STL at 3 and 6 months follow-up. This reinforces superior functional outcomes, as measured objectively using mfERG, by hastening SRF resorption in patients with acute CSC using STL.

Our study is limited by a definite period of follow up which might preclude the observation of recurrences and lack of microperimetric correlation. It would also have been preferable to employ the ETDRS chart for testing visual acuity.

Conclusion

To conclude, STL is a safe and effective therapeutic modality in acute CSC. It causes rapid improvement on SD-OCT which leads to better CS and mfERG values on follow up, as compared to spontaneous resolution of SRF, despite similar changes in BCVA. It may become the preferred first line of therapy in acute CSC to prevent functional damage associated with increased duration of the disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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