Original Article

Half-fluence photodynamic therapy in chronic central serous chorioretinopathy

ABSTRACT

Purpose: The aim of this study is to investigate the effect of half-fluence photodynamic therapy (PDT) in chronic central serous chorioretinopathy (CSC).

Materials and Methods: Forty-two eyes of 34 patients with chronic CSC and symptoms for at least 6 months were retrospectively reviewed. All eyes were treated with indocyanine green (ICG)-guided half-fluence PDT. The primary outcome measure was the proportion of eyes with complete resolution of subretinal fluid (SRF) on spectral domain-optical coherence tomography (SD-OCT). The secondary outcome measure was change in best corrected visual acuity (BCVA). SPSS v. 16 software was used for statistical analysis.

Results: The mean follow-up period was 12.5 ± 4.3 months. Twenty six (78.78%) eyes showed complete resolution of SRF ($P < 0.01$). BCVA increased by a mean of 0.43 to 0.42 log MAR ($P < 0.31$) at 12-month follow-up. Serous macular detachment height reduced from a mean of 166 μ to 40 μ ($P < 0.01$), and BCVA improvement of 1 line was seen in 16 eyes at 12 month follow-up visit. Ellipsoid line improvement was seen in 12 (36.36%) eyes compared to 5 (15.15%) eyes at the baseline visit ($P = 0.01$). Eyes with SD-OCT features of idiopathic serous-pigment epithelial detachment showed improvement of 0.12 logMAR in BCVA, as compared to irregular retinal pigment epithelium (0.01 logMAR) in 12 months duration.

Conclusion: Half-fluence PDT is an effective and safe method in the treatment of chronic CSC with stabilization or improvement of anatomical and functional outcomes.

Keywords: Best corrected visual acuity, chronic central serous retinopathy, half fluence photodynamic therapy, idiopathic serous pigment epithelial detachment, indocyanine green angiograpy, spectral domain optical coherence tomography

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by neurosensory retinal detachment caused by accumulation of serous fluid between photoreceptor outer segments and retinal pigment epithelium (RPE) in combination with pathological changes in RPE.[1] The disease often resolves spontaneously, however occasionally, the neurosensory detachment persists and leads to damage to the RPE and photoreceptors, along with visual impairment.[2] Chronic central serous chorioretinopathy (cCSC) is defined as persistence of this pathology for more than 6 months. The characteristic diffuse or multifocal leakage through the RPE on fluorescein angiography (FA) caused by defective or decompensated RPE was deemed responsible for detachment of the neurosensory retina.[3] Unlike acute CSC, chronic CSC may lead to further complications, such as diffuse RPE decompensation,[4] subretinal precipitates,[5] descending atrophic tracts,[6] cystoid macular degeneration,[7] secondary choroidal neovascularization (CNV),[8] and fibrous scarring,[2] which leads to poor visual prognosis. The increased use

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Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_6_17	

How to cite this article: Goyal A, Giridhar A, Gopalakrishnan M. Half-fluence photodynamic therapy in chronic central serous chorioretinopathy. Kerala J Ophthalmol 2016;28:125-30.

of indocyanine green angiography (ICGA) in chronic CSC had demonstrated that, in addition to RPE degeneration, choroidal circulation is primarily affected resulting in choroidal vascular hyperfluorescence.[9]

Various treatment modalities such as observation, medical therapy,[9,10] laser photocoagulation,[11,12] intravitreal bevacizumab injection,[13-15] and photodynamic therapy[16,17] have been attempted for the treatment of cCSC. Although bevacizumab improves the symptoms of cCSC through direct inhibition of vascular endothelial growth factor, a representative promoter of vascular permeability, due to high recurrence of cCSC, repeated injections are reported.[13]

PDT for the treatment of cCSC has been reported to be efficacious in improving visual acuity, reducing subretinal fluid (SRF), and decreasing recurrence rate in most patients by reducing choroidal exudation and inducing choriocapillary remodeling.[16,17] In long standing cCSC with foveal atrophy, modified PDT protocols, in terms of verteporfin dosage, fluence rate, the time course of delivery, or a combination thereof, may be more appropriate. We recently observed functional improvement without significant retinal or choroidal damage by reducing the fluence rate of PDT. In the present study, we investigated the efficacy and the rate of side effects of PDT therapy with a half-fluence rate for the treatment of cCSC.[18-20]

MATERIALS AND METHODS

We prospectively studied 33 eyes of 28 patients with symptomatic cCSC for at least 6 months. Patients studied between March 2010 and December 2014 were included in the study. Some of the inclusion criteria were (1) persistent symptoms for at least 6 months; (2) presence of SRF in the foveal region with or without pigment epithelial detachment (PED) on optical coherence tomography (OCT); (3) Presence of angiographic leakage on FA; (4) Abnormal dilated choroidal vasculature and choroidal vascular hyperpermeability or hypopermeability with an area of active leakage on ICGA corresponding to the leaking area on fundus fluorescein angiography (FFA). Patients who received any previous treatment, including PDT or focal thermal laser photocoagulation for CSC, or who had FA or ICGA findings of CNV, polyploidal choroidal vasculopathy (PCV), or other maculopathy on clinical examination were excluded. All patients were evaluated by one retina specialist. Diagnosis of CSC was based on clinical findings and ancillary tests such as ICGA, FFA, and spectral domain optical coherence tomography (SD-OCT). Distance visual acuity was assessed using the Snellens chart which was later converted to LogMAR by conversion tables. Macular SD-OCT, ICGA, and FFA (Heidelberg Engineering, Heidelberg, Germany) were performed in all patients prior to the treatment. Treatment with PDT was initiated once a complete ophthalmic assessment was done. The spot size of treatment was measured by comparing both ICGA and FFA images. The delivered laser energy, which was used during treatment sessions, was half of the standard dose (half-fluence PDT), i.e., 25 mJ/cm^2 over 83 s. Intravenous verteporfin was given at a dose of 6 mg/m^2 over 10 min, as recommended by the FDA. All patients were admitted to the hospital for the treatment and instructed to avoid sun exposure for 3 days posttreatment. Chart review of electronic medical records for these patients was done to collect appropriate data. Follow-up visits were at months 1, 3, 6, and 12 post treatment. OCT was done for all patients in all follow-up visits. The primary outcome measure was the proportion of eyes with complete resolution of SRF on SD-OCT. Secondary outcome measures were the changes in best corrected visual acuity (BCVA) and serous macular detachment (SMD) height, and the proportion of eyes that showed an increase of 1 line improvement in BCVA at the last visit. FFA and ICG were not done posttreatment because they showed improvement clinically and by OCT in all follow-up visits. Statistical analysis was performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). *P* value ≤0.05 was considered statistically significant.

RESULTS

We retrospectively analyzed 33 eyes of 28 patients diagnosed to have cCSC on ICGA and FFA. The mean follow-up period

Table 1: Baseline Patient Demographics and Clinical Characteristics

Age (years)	
Mean	48
Range	38-69
Sex, *n* (%)	
Male	27 (81.8%)
Female	6 (18.18%)
Laterality (patients)	
Bilateral	5
Unilateral	23
ICGA pattern, *n* (%)	
Diffuse hyperflorescence	27 (81.81%)
Discrete hypoflorescence	6 (18.18%)
FFA pattern, *n* (%)	
Diffuse hyperfluorescence	20 (60.6%)
Multiple leak hyperfluorescence	13 (39.39%)
RPE pattern on SD-OCT, *n* (%)	
Irregular RPE	24 (72.72%)
Idiopathic serous PED (IS-PED)	9 (27.27%)
BCVA (logMAR)	
Mean±SD	0.43±0.39
SRF height (microns)	
Mean±SD	166.42±52.02

Table 2: Frequency distribution of changes in BCVA and SRF height in 12 months followup

	Baseline	1 month	3 month	6 month	12 month	*P*
BCVA (logMAR)	0.43	0.43	0.40	0.38	0.39	0.31
SRF height (μm)	166.42	24.55	21.21	23.94	17.42	<0.001

*Wilcoxon signed rank test

Table 3:-Change in parameters in 12 months duration

Complete resolution of subretinal fluid on SD-OCT, *n* (%)	26 (78.78%)
BCVA change from baseline, *n*(%)	
Improvement >0.2 logMAR	13 (39.39%)
Improvement <0.2 logMAR	11 (33.33%)
Worsening	9 (27.27%)

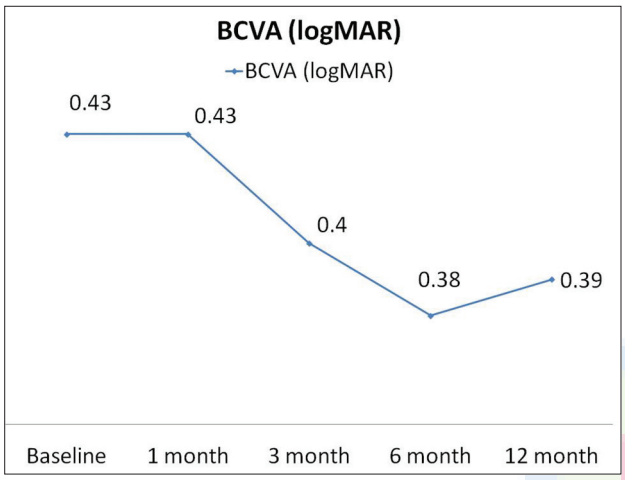

Figure 1: Change in best corrected visual acuity (logMAR) over 12 months duration

was 12.5 ± 4.3 months. Follow-up was done based on change on SD-OCT. Five (17.85%) patients had bilateral involvement. We treated all eyes with half fluence PDT.

Baseline demographics and clinical characteristics are shown in Table 1. BCVA improved from pretreatment a mean visual acuity of 0.43 to 0.39 log MAR ($P = 0.31$) at the final follow-up visit was not statistically significant [Table 2 and Figure 1]. Statistically significant complete resolution of SRF on SD-OCT was seen in 26 (78.78%) eyes ($P < 0.01$) at final follow-up visit and BCVA improvement of ≥1 line was seen in 16 eyes at 12-month follow-up visit. Worsening of BCVA was seen in 9 (27.27%) eyes at the final follow-up visit [Table 3].

SRF height showed statistically significant reduction in height from the pretreatment mean of 166 μ to 40 μ ($P < 0.01$) at the final follow-up visit [Figure 2 and Table 2]. Twenty-six (78.78%) eyes showed complete resolution of fluid at final follow-up visit. These eyes showed a complete resolution of the cCSC within 1 month of therapy, whereas mean BCVA improvement was delayed by more than 1 month of therapy.

At the site of the macular detachment, ellipsoid line on SD-OCT was preserved in only 5 eyes at the baseline visit. Restoration of ellipsoid line at the site previous macular detachment was seen in 7 out of remaining 28 eyes at final follow-up visit. Indiscriminate presence of SRF and posterior retinal cystoid degenerations were present in 6 (18.18%) eyes at the final follow-up visit. Recurrence of cCSC was seen in 1 eye after 24 months of follow-up. No other adverse event was in our study.

DISCUSSION

CSC is a common acquired maculopathy. Acute CSC usually resolves spontaneously with very good visual acuity.[21] However, cCSC may need treatment since vision can be permanently affected.[22]

Initially, Maumenee[23] in 1965 described a leak at the level of RPE and subsequently Gass[24] provided detailed description of the FA findings of the disease. Guyer *et al.*[8] suggested choroidal vascular hyperpermeability on ICGA with or without associated RPE active leaks, and that the neurosensory retina is only secondarily affected.

Laser photocoagulation was used for decades before the era of PDT. However, laser photocoagulation may not accelerate resolution and does not reduce the recurrence rate. In addition, it can be used only in acute CSR leak and may result in permanent visual defects.[11,12,26]

Recently, half fluence PDT with vertiporfin has been used widely for the treatment of cCSC, and studies have demonstrated beneficial outcomes in most patients.[20,25,28-34] Regarding the mechanism of PDT treatment for cCSC, it is hypothesized that PDT induces selective and transient occlusion of choriocapillaries, which is the main source of exudation.[30] Still, true pathophysiology of cCSC is not completely understood.[31]

To improve PDT safety, we found that half fluence PDT is a safe and effective treatment alternative for patients with cCSC, as anatomical success of half-fluence PDT is 79–91% with minimal side effects or catastrophic visual loss.[33] In our study, 78.78% of the eyes showed significantly complete resolution of SRF at 1 month follow-up after the treatment, which is comparative to other studies which showed

80%[28,30,32] to 100%[20,27,31,33,34] results of complete resolution of SRF.

ICGA for cCSC showed disturbance of choroidal perfusion and suggested that choroidal hyperpermeability might be the origin of cCSC.[22] Yannuzzi *et al*.[35] introduced ICGA-guided PDT as the TAP study on areas of visible hyperpermeability on ICGA. Most studies documented complete resolution of SRF inintense hyperfluorescence as compared to weak hyperfluorescence group,[20,30-32] however, none had documented presence of hypofluorescence on ICGA. On the contrary, we found 2 patterns of ICGA—diffuse hyperfluorescence in 81.81% [Figure 3] and discrete hypofluorescence in 18.18% cases [Figure 4]. Both diffuse hyperfluorescence and discrete hypofluorescence groups had shown nearly the same percentage (77% and 83%, respectively) of complete resolution of SRF at the last follow-up visit, which is contrary to other studies which showed better results in the intense hyperfluorescence group.[20,32]

Reibaldi *et al*.[31] studied standard fluence versus low-fluence PDT and showed significant comparative improvement in BCVA of 0.19 and 0.3, respectively, in these groups. Lim *et al*.[20] showed BCVA improvement of 0.21 on half-fluence PDT. In the study done by Nicolo *et al*.[32] on half dose PDT and Rosenthal *et al*.[31] on comparison between half-dose vs. half-fluence PDT, there was no significant change in final BCVA. Thus, from these studies we conclude that improvement in BCVA is better in half-dose or half-fluence PDT compared to that with standard-dose treatment, which can be attributed to more severe choriocapillary hypoperfusion, choroidal neovascularization, and foveal atrophy due to standard-fluence PDT.[25] In our study also, though there was no significant change of 0.04 in BCVA at the 12-month follow-up visit, yet stabilization or worsening was seen in 9 (27.27%) eyes only, which can be attributed to prolonged duration of CSC of more than 2 years which might result in permanent damage to photoreceptors, and hence, permanent visual loss.[25]

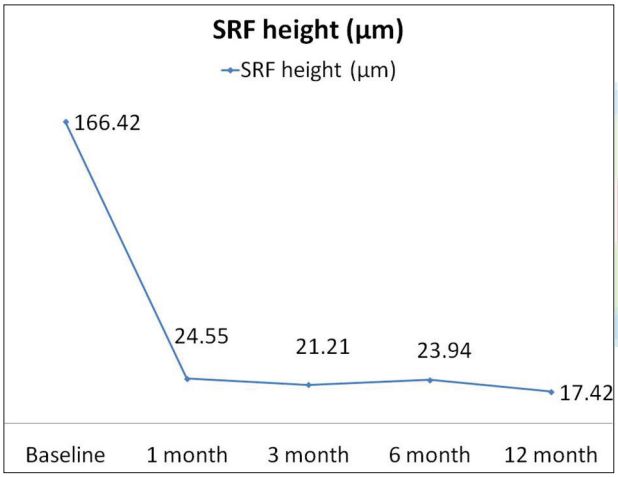

Figure 2: Change in subretinal fluid height (µm) over 12 months duration

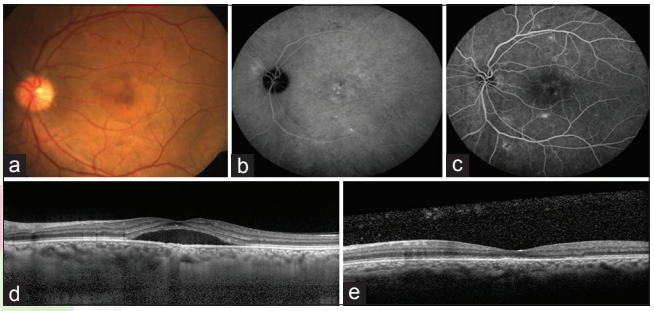

Figure 3: Case of chronic CSR before and after half-fluence PDT – (a) Clinical picture with coin shaped hypopigmented lesion in macula, (b) ICGA with central macular diffuse hyperfluorescence, (c) FFA with diffuse hyperfluorescence in area corresponding to ICGA, (d) SD-OCT showing subretinal fluid before half fluence PDT, (e) SD-OCT after 12 months of half fluence PDT showing complete resolution of SRF with persisting loss of ellipsoid line in macula

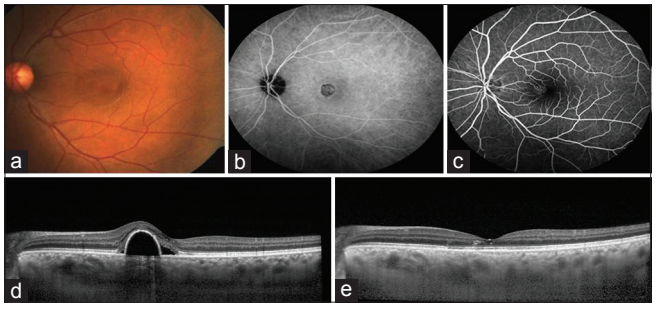

Figure 4: Case of chronic CSC showing (a) clinical picture with circular hypopigmented lesion in macula, (b) ICGA with area discrete hypofluorescence in macula, (c) FFA with area of diffuse hyperfluorescence corresponding to ICG hypofluorescent area, (d) SD-OCT before half fluence PDT with large idiopathic serous pigment epithelial detachment (IS-PED) in area corresponding to hypofluorescent area on ICGA with presence of SRF, (e) SD-OCT after 12 months of half fluence PDT showing complete resolution of IS-PED with restoration of ellipsoid line

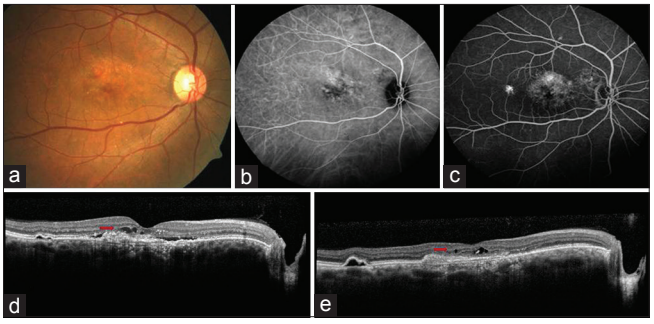

Figure 5: Case of chronic CSC showing (a) Clinical picture with orange color lesion superior to fovea, (b) ICGA showing diffuse hyperfluorescence superior to fovea, (c) FFA with diffuse hyperfluorescence corresponding to ICGA lesion, (d) SD-OCT before half-fluence PDT with posterior cystoid retinal degeneration (arrow), subretinal fluid, long standing RPE decompensation in fovea and IS-PED in temporal macula, (e) after half fluence PDT with persisting posterior cystoid retinal degeneration (arrow), RPE defect and IS-PED, though SRF is completely resolved

Out of 6 eyes with posterior cystoid retinal degeneration [Figure 5], only 3 showed dry macula at 12-month follow-up. All eyes with posterior cystoid retinal degeneration were seen to have diffuse hyperfluorescence on ICGA. Nicolo *et al*.[32] suggested that posterior cystoid retinal degeneration originates from chorioretinal adherent lesions derived from long-standing RPE decompensation as well as choroidal hyperpermeability. We observed 1 recurrence in diffuse hyperfluorescence group, which was also commonly seen in other studies.[20]

In our study, we did not find any complication such as CNVM, which is known to be a rare complication secondary to cCSC,[30] and also reported after standard PDT related to secondary hypoxic damage and RPE changes.[36-38] The main limitation of our study is its retrospective nature, small follow-up, lack of randomization, and lack of comparative study design, which might have led to overestimating or underestimating the outcome of the treatment. Therefore, further investigation is needed to determine whether there could be difference in treatment outcomes, complications, and recurrence rates in long-term follow-up after half fluence PDT according to the degree of varied choroidal florescence on ICGA.

CONCLUSION

In conclusion, resolution of SRF might be expected in eyes with cCSC, regardless of the intensity of choroidal florescence after half fluence PDT. Half-fluence PDT is an effective and safe method in the treatment of cCSC with stabilization or improvement of anatomical and functional outcomes. We should, however, be aware of persistence or recurrence of disease in eyes with posterior cystoid retinal degeneration.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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