Short-Term Effects of Photodynamic Therapy on Segmentation of Retinal Layers in Central Serous Chorioretinopathy

Abstract
Background: The present study aims to evaluate the effect of photodynamic therapy (PDT) on the thickness of segmentation layers of the retina in cases with central serous chorioretinopathy (CSCR).

Materials and Methods: This was a prospective, observational study on cases with CSCR who were candidates for PDT therapy. All patients had undergone at least 1 month of conservative management without satisfactory resolution. PDT was carried out according to the safe half-dose therapy scheme. Spectral-domain optical coherence tomography was employed to evaluate the changes in morphology and segmentation of retinal layers. Patients were followed up for 3 months. Results: Twenty-seven cases (18 males and 9 females) were included. Age of the patients varied from 39 to 59 years (mean: 46.61 ± 12.48 years). Cases were followed for 92.17 ± 3.28 days. Sixteen cases had functional and anatomical improvement by the treatment. Changes in overall retinal (377.39 ± 61.36 to 323.61 ± 71.36; P = 0.004) and all outer retinal segmentation layers including outer plexiform layer (34.93 ± 10.07 to 29.25 ± 6.12; P = 0.008), outer nuclear layer (63.52 ± 30.44 to 46.44 ± 20.62; P = 0.017), and retinal pigment epithelium (40.66 ± 37.73 to 23.78 ± 29.33; P = 0.016) were statistically significant. On the contrary, inner retinal segmentation layers, especially retinal ganglion cell (RGC) layer (38.29 ± 16.63 to 37.26 ± 16.18; P = 0.387), remained statistically unchanged.

Conclusion: We postulate that PDT alleviates outer retinal edema where fluid accumulation occurs mostly, whereas it does not alter inner retinal and especially RGC layer. These findings may indicate that short-term atrophy of the inner retina did not occur following PDT and may point toward safety of this method for cases with CSCR.

Keywords: Central serous chorioretinopathy, Tomography, Optical Coherence, photodynamic therapy, Retinal Ganglion Cells, image processing

Introduction
Central serous chorioretinopathy (CSCR) is a choroidoretinal disease with undetermined etiology that results in retinal serous detachment, especially in the macula, due to fluid accumulation between the two layers of the retinal pigment epithelium (RPE) and the photoreceptor layer. The disease has two forms, acute or chronic. The acute form of the disease is often self-limiting accompanied by spontaneous regression in 85% of cases over 3 months. In the chronic form (often more than 6 months), there is persistent subretinal fluid (SRF) that may lead to RPE atrophy, retinal cystoid changes, and persistent decreased vision.[1-3]

As regards treatment of CSCR, treatment options include lessening risk factors (such as steroid use),[4] drug therapy,[5] conventional topical laser,[6] and photodynamic therapy (PDT).[7-10] PDT causes absorption of SRF by reducing the permeability of choroidal vessels.[11,12] It has also been associated with serious complications, such as choroidal ischemia, RPE atrophy, and iatrogenic choroidal neovascularization.[11]

One of the possible adverse effects of PDT on the retinal layers may cause temporary or permanent damage to the retinal tissue and cell integrity.[14-20] Recent advances in optical coherence tomography (OCT) technology have made it possible to isolate segmentation retinal layers and evaluate their changes.

In the literature, there is evidence of damage to photoreceptors and RPE cells,[14,15] inner/outer segment (IS/OS) of photoreceptors, and outer nuclear layer (ONL)[18-20] following PDT. Due to the growing use of PDT in CSCR cases, and its various effects on different layers of the retina, the present study aims to evaluate the effect of PDT on
the thickness of segmentation layers of the retina of such cases.

**Materials and Methods**

**Settings and ethics**

This prospective, observational study was conducted in Isfahan Province at Didavarvan Eye Clinic and Feiz Eye Hospital. Eligible cases were enrolled consecutively from November 2016 to September 2018.

The research was undertaken in conformity with the tenets of Helsinki Declaration and standards of good clinical practice (the International Conference on Harmonization of Technical Requirements for registration of pharmaceuticals for human use). The protocol was critically reviewed and approved by the Institutional Ethics Committee of Isfahan University of Medical Sciences (IUMS), and all patients gave signed informed consent before inclusion. The research protocol on the cohort was merely observational and did not interfere with routine treatments measures of patients. Hereby, only CSCR cases who were primarily candidates for PDT were included in this observational research as an imaging surveillance.

**Patients and participation criteria**

CSCR cases who were candidates for PDT therapy were considered for possible inclusion. Patients were included if they had diagnosis of CSCR based on the clinical evaluation and imaging evidence as needed (OCT, etc.). All included cases had serous neurosensory detachment without any evidence of hemorrhage or exudation.

All the patients had undergone at least 1 month of conservative management (observation, life style modification, and medical treatment) without satisfactory resolution. Indeed, patients were the candidates for PDT therapy if they had no significant improvement of OCT findings or visual function after 1 month of conservative management. All the cases should have been PDT-naïve. Exclusions were as follows: (i) history of any previous laser photocoagulation and/or intraocular surgery/injection; (ii) ocular/visual morbidity in the evaluated eye: (a) significant macular diseases; (b) presence of iris neovascularization; (c) history of glaucoma or ocular hypertension; (iii) ocular/visual morbidity in the contralateral eye except CSCR; (iv) significant media opacity; (v) systematic comorbidities, e.g., pregnancy, serum creatinine ≥3 mg/dl, and diabetes mellitus.

**Protocols and interventions**

PDT was carried out according to the safe half-dose therapy scheme using verteporfin (Visudyne®, 3 mg/m², injected intravenously for 8–10 min). Five minutes afterward, laser with the following settings were applied: Light dose of 50 J/cm²; light intensity of 600 mW/cm²; application time of 83 s; maximum absorption of 689 nm; laser spot size of 2000–4000 µm in diameter. Laser was applied on the macular foci where hyperperfusion was apparent in indocyanine green (ICG) images. Spectral-domain OCT with the adherent latest application (Spectralis, Heidelberg Engineering, GmbH) was utilized for the evaluation of changes in the morphology and segmentation of retinal layers.

**Examinations**

Before intervention, thorough ophthalmologic assessment (best-corrected visual acuity [BCVA], refraction, slit lamp biomicroscopy, tonometry, fundoscopy, and fundus photography) and OCT, ICG, and fluorescence angiography imaging were performed. All examinations were repeated at week 12 after the intervention. To detect possible adverse complications, visits were planned weekly.

**Measures**

The primary outcome measure was the pre-/post-PDT segmentation layer thicknesses. Anatomic and functional response (second-line improvement of visual acuity) to treatment was the secondary outcome measure.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation and qualitative variables are presented as number (percent). Before/after comparison for each variable was performed by paired t-test. Tests were two-tailed with an alpha of 5%. SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was incorporated.

**Results**

Twenty-seven cases (18 males and 9 females) were included. Age of the patients varied from 39 to 59 years (mean: 46.61 ± 12.48 years). Cases were followed for 92.17 ± 3.28 days. Sixteen cases had functional and anatomical improvement by the treatment.

Before–after values of overall and segmentation thicknesses (at baseline and week 12) are shown in Table 1. As it is shown, changes in overall retinal (377.39 ± 61.36 to 323.61 ± 71.36; \( P = 0.004 \)) and all outer retinal segmentation layers including outer plexiform layer (34.93 ± 10.07 to 29.25 ± 6.12; \( P = 0.008 \)), ONL (63.52 ± 30.44 to 46.44 ± 20.62; \( P = 0.017 \)), and RPE (40.66 ± 37.73 to 23.78 ± 29.33; \( P = 0.016 \)) were statistically significant. On the contrary, inner retinal segmentation layers, especially retinal ganglion cell (RGC) layer (38.29 ± 16.63 to 37.26 ± 16.18; \( P = 0.387 \)), remained statistically unchanged.

No PDT complications such as macular hemorrhage, retinal atrophy/scarring, choroidal ischemia, and RPE atrophy were observed.

**Discussion**

Resolution of SRF, visual improvement, and prevention of recurrence are the mainstay goals in the management of
In this article, we reported a prospective case series, evaluated the relationship between the integrity of the photoreceptor microstructures and retinal sensitivity after half-dose PDT in eyes with CSCR. They found that the visual improvement was correlated with the recovery of the IS/OS and cone OS tips line.

Interpretation of our results suffers from some limitations. First, we should acknowledge the inadequate sample size that deprived the study from achievement of high statistical power. Another point was the short duration of follow-up. This limits our judgment on the long-term effects of PDT on thickness of RGC and other layers of the retina.

Conclusion

We showed that PDT decreases the overall and outer retinal thickness. This finding was consistent as regards all segmentation layers of outer retina, where the fluid accumulates more severely. On the contrary, we found that inner retina and its segmentation layers remain unchanged after PDT; this is a finding that points toward safety of this method for cases with CSCR.

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Conflicts of interest
There are no conflicts of interest.

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