Original Article

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

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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.[13]

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

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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 Didavaran 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 candidated 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.[4] 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/m^2, injected intravenously for 8–10 min). Five minutes afterward, laser with the following settings were applied: Light dose of 50 J/cm^2; light intensity of 600 mW/cm^2; 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

Table 1: Before/after thickness of retina and its segmentation layers in µm

	Mean±SD	*P* (paired *t*-test)
Overall retinal thickness		
Before	377.39±61.36	0.004
After	323.61±71.36	
Retinal nerve fiber layer		
Before	39.44±26.96	0.053
After	37.22±25.83	
Retinal ganglion cell layer		
Before	38.29±16.63	0.387
After	37.26±16.18	
Inner plexiform layer		
Before	32.593±10.98	0.65
After	32.15±10.21	
Inner nuclear layer		
Before	37.18±10.26	0.102
After	35.07±7.93	
Outer plexiform layer		
Before	34.93±10.07	0.008
After	29.25±6.12	
Outer nuclear layer		
Before	63.52±30.44	0.017
After	46.44±20.62	
Retinal pigment epithelium		
Before	40.66±37.73	0.016
After	23.78±29.33	

SD: Standard deviation

CSCR cases. In this regard, during the last decade, PDT has played a pivotal role alone or in combination with medical modalities.[11-13]

The present prospective case series revealed that PDT sessions has beneficial short-term effects on anatomical (central thickness and volume of the macula) and functional (BCVA) outcomes of CSCR. Major concerns have always been about the side effects of PDT in such cases. The major issue herein is the possibility of retinal atrophy and damage due to destructive properties of laser and abrupt alteration of retinal vasculature due to photo-activation of verteporfin. As is known, the accumulation of fluid during the process of CSCR occurs more severely within the outer layers of the retina. Our OCT data about segmentation layers of the retina support the notion that as CSCR causes fluid accumulation more in the outer retina, PDT decreases thickness of the outer layers of the retina. Such decrement of retinal thickness leads to anatomical and functional improvement. On the one hand, there is a possibility of concomitant atrophy in the outer retinal layers. In line with our short-term results, in the literature, there is evidence on long-term damage to photoreceptors and RPE cells,[14,15] IS/OS of photoreceptors, and ONL (18–20) following PDT.

It is to be noted that RGC layer may not be involved in the process of primary edema, and our main concern as regards, this layer would be avoiding from its undesirable atrophy. As we found that changes in thickness of this layer following PDT were not statistically significant. Other studies did not show atrophy of this layer flowing PDT as well.[18-20]

In experimental models, studies have shown that PDT exerts less damage to the retinal layers than laser photocoagulation, although damage to photoreceptors and RPE cells has been pronouncedly observed following this procedure.[14,15] In 2002, Schlotzer-Schrehardt *et al*. found no histological evidence of damage to human retinal cells after PDT,[16] but this study posed a serious challenge with the results of a 2004 study by Arnold *et al*.[17] In this article, the authors reported that a number of age-related macular degeneration patients experienced acute and severe vision loss, 1 week after PDT.[17]

Histological examination by Duncan *et al*. in another experimental study on rats showed that 1 week after PDT, severe damage to retinal and RPE layers occurred.[18] They showed that the thickness of the ONL in the treated eyes with PDT decreased significantly with histological changes compared to the control group. There has also been a decrease in IS/OS of photoreceptors.[18]

Matušková *et al*. in their retrospective review of 32 CSCR cases managed by half-dose PDT found that the most important predictive factor was baseline visual acuity. The important anatomical change detected using OCT was found to be thinning of the ONL.[19] Fujita *et al*., in their 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.[20]

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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