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Comparative Study of Subjects with Chronic Central Serous Chorioretinopathy Undergoing Half-Dose or Time-Reduced Photodynamic Therapy

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Purpose: To compare the clinical outcomes of reduced fluence (time-reduced) photodynamic therapy (PDT) and half-dose PDT in treating chronic central serous chorioretinopathy (CSC).

Methods: Medical records of patients who underwent half-dose or reduced fluence PDT for chronic CSC were reviewed. The clinical outcomes of 34 eyes that underwent half-dose PDT and 39 eyes that underwent reduced fluence PDT were compared.

Results: Six months after treatment, complete absorption of subretinal fluid was observed in 29 of 34 eyes (85.3%) in the half-dose PDT group and 36 of 39 eyes (92.3%) in the reduced fluence PDT group ($p = 0.46$). Twenty-one of 34 (61.8%) eyes in the half-dose PDT group and 27 of 39 (69.2%) eyes in the reduced fluence PDT group achieved visual improvement of more than one line in the Snellen chart ($p = 0.62$). Focal retinal pigment epithelium degeneration after treatment was noted in 7 of 27 eyes (25.9%) in the half-dose PDT group and 10 of 30 (33.3%) eyes in the reduced fluence PDT group ($p = 0.58$).

Conclusions: Reduced fluence PDT showed a favorable outcome, similar to that of half-dose PDT, in treating chronic CSC. Because of its convenient preparation and application, reduced fluence (low-fluence) PDT might be an alternative treatment modality in treating chronic CSC.

Keywords: Central serous chorioretinopathy; Photodynamic therapy; Verteporfin

Introduction

Central serous chorioretinopathy (CSC) causes visual disturbances, including micropsia, metamorphopsia, central scotoma,

reduced visual acuity, and loss of contrast sensitivity [1]. Most patients with episodes of CSC experience spontaneous resolution within 3 to 4 months. However, some patients undergo long-standing visual symptoms with chronic neurosensory retinal detachment and retinal pigment epithelium (RPE) atrophy [2,3].

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Laser photocoagulation has been employed to enhance absorption of subretinal fluid and shorten symptom duration by directly sealing off the leakage point [4]. Although laser photocoagulation results in a shortened disease course, direct thermal damage of the RPE frequently hampers effective management of CSC with a subfoveal/juxtafoveal leakage point. In eyes that show diffuse oozing, laser photocoagulation may not be a suitable treatment modality because localization of the leaking point is difficult. Photodynamic therapy (PDT) with verteporfin, which causes less thermal damage, has resulted in beneficial visual outcomes in most studies of patients with chronic CSC [5-7]. However, several studies have shown that conventional PDT, traditionally used to treat choroidal neovascularization or polypoidal choroidal vasculopathy, may cause RPE atrophy, choroidal ischemia, and transient reduction in macular function [5,8,9]. Because subjects with episodes of CSC have relatively good visual acuity and a majority of patients with CSC have fair prognosis, some investigators have attempted to minimize retinal damage by reducing the dose of verteporfin or laser fluence [10-13]. Although both low-fluence PDT and half-dose PDT have demonstrated good clinical outcomes in treating CSC, preparation for these procedures is inconvenient, resulting in over-treatment or under-treatment. Thus, some investigators have adopted reduced fluence PDT, which reduces the laser emission time. The authors designed this study to compare the clinical results of reduced fluence PDT and half-dose PDT in treating chronic CSC.

Materials and Methods

The medical records of 84 eyes in 80 patients who underwent half-dose or reduced fluence (time-reduced) photodynamic therapy for chronic CSC at the Samsung Medical Center between January 2007 and June 2010 were reviewed. Among these subjects, 73 eyes of 69 patients (86.9%) who completed 6-months of follow-up were included in the present study.

The institutional review board approved this study protocol. Diagnosis of CSC was based on clinical findings of fundoscopy, fluorescein angiography (FA), indocyanine green (ICG) angiography (Heidelberg Retina Angiography; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT; Stratus, Model 3000, Carl Zeiss Ophthalmic Systems, Dublin, CA, USA). Eyes with chronic CSC,

considered as documented subretinal fluid (SRF) on OCT with persistent or progressive visual symptoms for more than 3 months, were included. Prior history of PDT or eyes with any evidence of macular abnormality other than CSC, such as choroidal neovascularization, polypoidal choroidal vasculopathy, macular edema from diabetic retinopathy, retinal vein obstruction, or uveitis were excluded. Informed consent for PDT was obtained from all patients before treatment. Patients treated from January 2007 to October 2009 were treated with half-dose PDT, and patients who visited from November 2009 to June 2010 underwent reduced fluence PDT (time reduced). The authors changed the treatment protocol from half-dose PDT to reduced fluence PDT because of 1) simplicity of preparation and 2) convenience in treating 2 distant lesions or both eyes at once. No intended choice of physician was included in the choice of PDT protocols.

Both half-dose PDT and reduced fluence PDT were performed based on indocyanine green angiography (ICGA). Half-dose PDT (3 mg/m² of verteporfin) was performed in the same manner as described in previous studies, with a power of 600 mW/cm² delivered with a 689 nm diode laser for 83 seconds. The laser was started at 10 minutes after intravenous injection of 3 mg/m² verteporfin (total delivered energy: 50 J/cm²) to the area of choroidal hyperpermeability observed in ICGA. For reduced-fluence PDT, the authors lowered the light energy via reduced delivery time instead of adjusting laser power. Laser of the same power (600 mW/cm²) was delivered for a shortened duration (50 seconds). Thus, the total delivered light energy was reduced from 50 J/cm² to 30 J/cm² in the reduced-fluence PDT group. As with conventional PDT, all patients were instructed to avoid strong light for 2 days. Subjects were assessed before treatment and at months 1, 3, and 6 after PDT. At each visit, best-corrected visual acuity and intraocular pressure were measured, and a dilated fundus examination was conducted. OCT was performed at baseline and 1 month after PDT. With any evidence of SRF at a prior visit, OCT was employed at every visit until complete disappearance of SRF. RPE atrophy was evaluated under dilated fundus examination by one physician (SWK) each visit. Anatomical success was defined as the absence of SRF at the 6-month visit on OCT. Visual improvement and deterioration were defined as visual gain > one line and visual loss > one line. The main outcome measures of the present study were anatomic success rate and change of best corrected visual acuity (BCVA). Development of focal RPE degeneration,

defined as pigmentary changes with subretinal deposition of yellow orange pigment under slit-lamp biomicroscopy, was also assessed [5]. For statistical analysis, best-corrected visual acuity (decimal) was converted to a logarithm of the minimum angle of resolution (logMAR) scale. Student *t*-test and Fisher's exact test were performed using the SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). The odds ratio of anatomic and visual outcomes was determined via multivariate logistic regression analysis using the SPSS software version 18.0 (SPSS Inc.). *p*-values < 0.05 were considered statistically significant.

Results

The clinical characteristics of patients at the initial examination (baseline) are shown in Table 1. Average age was 49.09 ± 8.44 years in the half-dose PDT group and 50.59 ± 8.81 in the reduced fluence PDT group. No significant difference was observed between the 2 groups ($p = 0.46$). Baseline BCVA was 0.37 ± 0.46 logMAR in the half-dose PDT group and 0.28 ± 0.22 logMAR in the reduced fluence PDT group, with no significant difference ($p = 0.31$). The male to female ratio

was 29:5 in the half-dose PDT group and 35:7 in the reduced fluence PDT group. Systemic hypertension was noted in 6 subjects (17.6%) in the half dose PDT group and in 6 subjects (15.4%) in the reduced fluence PDT group. Significant differences in the sex ratio and systemic hypertension were not noted.

At 6 months after PDT, anatomic success was achieved in 29 of 34 eyes (85.3%) in the half-dose PDT group and 36 of 39 eyes (92.3%) in the reduced fluence PDT group ($p = 0.46$). Both treatments showed significant improvements in BCVA after 6 months, with 0.37 ± 0.46 logMAR at baseline to 0.18 ± 0.26 logMAR in the half-dose PDT group and 0.28 ± 0.22 logMAR at baseline to 0.16 ± 0.25 logMAR in the reduced fluence PDT group ($p < 0.001$ and < 0.001 , respectively) (Table 2). Twenty one of 34 eyes (61.8%) in the half-dose PDT group and 27 of 39 eyes (69.2%) in the reduced fluence PDT group achieved visual improvement of more than one line in the Snellen chart ($p = 0.62$). Meanwhile, 3 of 34 eyes (8.8%) in the half-dose PDT group and 5 of 39 eyes (12.8%) in the reduced fluence PDT group lost more than one line of Snellen visual acuity ($p = 0.72$). Development of focal RPE degeneration was observed in 7 of 27 eyes (25.9%) in the half-dose PDT group and 10 of 30 eyes (33.3%) in the reduced fluence

Table 1. Demographic characteristics comparing the half-dose photodynamic therapy (PDT) group and the reduced fluence (time reduced) PDT group

	Half-dose PDT	Reduced fluence PDT	<i>p</i> -value
No. of eyes	34	39	
Age (years)	49.09 ± 8.44	50.59 ± 8.81	0.46*
Sex			0.76†
Male	29	32	
Female	5	7	
Systemic hypertension (n, %)	6 (17.6)	6 (15.4)	1.00†
Visual acuity (logMAR)	0.37 ± 0.46	0.28 ± 0.22	0.31*
Symptom duration (months)	10.44 ± 10.24	40.56 ± 8.47	0.96*
Recurrent CSC (n, %)	9 (26.5)	13 (33.3)	0.61†
Presence of RPE atrophy (n, %)	7 (20.6)	9 (23.1)	1.00†
Presence of PED (n, %)	9 (26.5)	15 (38.5)	0.32†
Prior treatment for CSC (n, %)			
Intravitreal injection of anti-VEGF agent	4 (11.8)	2 (5.1)	0.41†
Focal laser photocoagulation	4 (11.8)	7 (17.9)	0.53

Values are presented as mean $\pm$ SD unless otherwise indicated.

CSC = chronic central serous chorioretinopathy; RPE = retinal pigment epithelium; PED = pigment epithelium detachmet; VEGF = vascular endothelium growth factor.

*Tested with student *t*-test; †Tested with Fisher's exact test.

Table 2. Outcomes of half-dose photodynamic therapy (PDT) and reduced fluence (time reduced) PDT after 6 months

	Half-dose PDT (n = 34)	Reduced fluence PDT (n = 39)	<i>p</i> -value
Anatomical success (n, %)	29 (85.3)	36 (92.3)	0.46*
BCVA (logMAR)	0.18 ± 0.26	0.16 ± 0.25	0.80†
VA improvement more than 1 Snellen line (n, %)	21 (61.8)	27 (69.2)	
No change (within 1 Snellen line) (n, %)	10 (29.4)	7 (17.9)	
VA deterioration more than 1 Snellen line (n, %)	3 (8.8)	5 (12.8)	
Development of RPE atrophy (n, %)	7 (20.6)	10 (25.6)	0.58*

Values are presented as mean ± SD or n (%) unless otherwise indicated.

BCVA = best corrected visual acuity; VA = visual acuity; RPE = retinal pigment epithelium.

*Tested with Fisher's exact test; †Tested with student *t*-test.

Table 3. Prognostic factors associated with anatomical success rate and visual outcomes at 6 months after half-dose or reduced fluence photodynamic therapy (PDT) for central serous chorioretinopathy

	Half-dose PDT (n = 34)						Reduced fluence PDT (n = 39)					
	Anatomical success		Visual gain > 1 line		Visual loss > 1 line		Anatomical success		Visual gain > 1 line		Visual loss > 1 line	
	<i>p</i> -value*	OR	<i>p</i> -value*	OR	<i>p</i> -value*	OR	<i>p</i> -value*	OR	<i>p</i> -value*	OR	<i>p</i> -value*	OR
Sex	0.83	0.51	0.30	0.20	0.85	0.46	1.00	0.00	0.31	0.30	1.00	0.00
Age (years)	0.05	0.76	0.17	1.10	0.13	1.51	0.83	1.02	0.33	1.05	0.25	0.94
Systemic hypertension	0.09	0.00	0.62	0.49	1.00	0.00	1.00	0.00	0.71	0.65	1.00	0.00
Duration of symptoms	0.88	0.99	0.16	1.10	0.80	1.11	0.93	0.99	0.27	0.95	0.63	1.04
Prior history of CSC	0.09	129.54	0.34	0.33	1.00	0.00	0.25	6.57	0.30	0.39	0.72	1.55
Bilaterality	0.18	8.77	0.07	8.12	0.93	1.17	1.00	0.00	0.43	0.44	0.55	2.13
Presence of PED	0.07	93.31	0.15	6.05	0.63	0.36	0.22	7.12	0.95	0.94	0.64	1.82

Odds ratios (ORs) are adjusted.

OR = odds ratio; CSC = chronic central serous chorioretinopathy; PED = pigment epithelium detachment.

*Tested and calculated with multivariate logistic regression analysis.

PDT group, with no statistical significance ($p = 0.58$).

In the subgroup analysis, no significant difference was observed in success rate based on sex, systemic hypertension, presence of pigment epithelium detachment (PED), duration of symptoms, prior episode of CSC, and bilateral involvement in both the reduced fluence PDT group and half-dose PDT group (Table 3). In the half-dose PDT group, the anatomical success rate tended to decrease among older subjects ($p = 0.045$). However, visual outcomes did not vary according to age (Table 3).

Discussion

This study revealed that both half-dose PDT and time reduced PDT showed favorable outcomes in treating chronic

CSC. Both groups showed a high anatomical success rate (85.3% in half-dose PDT and 92.3% in reduced fluence PDT) and improved visual acuity (0.18 ± 0.26 logMAR in half-dose PDT and 0.16 ± 0.25 logMAR in reduced fluence PDT). There was no observed difference in the rate of developing focal RPE degeneration after treatment. Although time reduced PDT showed a slightly higher anatomical success rate (85.3% in half-dose PDT and 92.3% in reduced fluence PDT), this difference was not statistically or clinically significant. Previous studies have shown that complete subretinal fluid reabsorption in eyes with chronic CSC was seen in 91% of eyes after low-fluence PDT and 79% of eyes after standard-fluence PDT [13]. Other investigators reported that complete resolution of serous detachment was observed in 89.6% of eyes with chronic CSC after half-dose PDT [11]. These clinical outcomes are similar to our findings. RPE alteration

was also observed in 20.6% of cases after half-dose PDT and in 25.6% of cases after reduced fluence PDT ($p = 0.58$). Although the rate of developing focal RPE degeneration after treatment was higher in the reduced fluence PDT group, we believe there is no difference between the 2 groups because 7 eyes (17.9%) in the reduced fluence PDT group had a history of prior laser photocoagulation compared to 4 eyes (11.8%) in the half-dose PDT group. It is difficult to compare PRE atrophy because CSC itself causes RPE alteration, and RPE alteration could be masked in eyes with subretinal fluid. Our results may suggest that reduced fluence PDT has a similar adverse effect on RPE.

Since Yannuzzi et al. [7] adopted PDT to treat chronic CSC, this treatment modality is still applied widely. Because CSC is generally a self-limiting disease with limited visual impairment, some investigators suspect that potential hazards of PDT exist, such as damage to the retinal pigment epithelium, transient reduction of macular function, and choroidal ischemia [8,9]. Thus, modifications of this modality were designed, such as half-dose PDT and low-fluence PDT. These modalities have shown favorable results in treating CSC [11,14]. Half-dose PDT, which reduces the amount of verteporfin administration, and low-fluence PDT, which reduces the laser power, have been designed and widely adopted. Our current study indicates that reduced fluence PDT, which reduces the total amount of laser energy per area by reducing the laser application time, provides a comparable outcome with half-dose PDT. Both half-dose PDT and reduced fluence PDT show favorable clinical outcomes and changes in the RPE. However, these treatments require special preparation, including adjusting the amount of verteporfin administration in half-dose PDT and adjusting the setting of laser devices in reduced fluence PDT. PDT is still a useful treatment modality for treating polypoidal choroidal vasculopathy, which requires full-dose, full fluence PDT [15]. Because the laser device for PDT is used to treat eyes with polypoidal choroidal vasculopathy as well as eyes with CSC, additional instrument adjustments may lead to over-treatment or under-treatment in the clinical setting by unintentional minor negligence. However, time reduced PDT does not require any adjustments in preparation or time to initiate laser application. Thus, time reduced PDT may reduce the potential hazards of over-treatment or under-treatment. Furthermore, reduced fluence PDT has merits in treating eyes with 2 or more laser spots because this modality requires less time (50 seconds) than either half-

dose PDT or low-fluence PDT (83 seconds). Reduced treatment time allows distant leak points to be treated in a similar circulatory phase of verteporfin. If two or more targets exist, shortening the laser irradiation time may help clinicians to treat each target and avoid exposing the fovea to the laser source. Shorter treatment time allows patients with bilateral involvement of chronic CSC to be treated with similar retinal verteporfin concentration.

The optimal duration of laser radiation in the reduced fluence PDT group may be an issue. Eyes showed a slightly higher rate of visual improvement (92.3% in time reduced PDT group vs. 85.3% in half-dose PDT group), but they also showed a slightly higher rate of visual deterioration (12.8% in time reduced PDT group vs. 8.8% in half-dose PDT group), although there was no statistical significance. Thus, further adjustments in duration might be necessary.

This study has a few limitations. The first involves estimation of focal RPE degeneration. This study aimed to review the medical records of patients with chronic CSC. If subretinal fluid exists, RPE changes are difficult to define. It was also difficult to measure the degree of RPE degeneration before and after PDT, partly because most patients underwent treatment before spectral-domain optical coherence tomography was available [16,17]. Thus, RPE atrophy was defined based on slit-lamp biomicroscopy, which is subjective. The second limitation involves the retrospective design of this study. We applied half-dose PDT from January 2007 to October 2009 and reduced fluence PDT from October 2009 to the present time. Although half-dose PDT was not recently performed in our clinic, we believe this does not affect clinical outcomes because both treatment modalities were applied to similar clinical settings, with the same clinician (SWK), same inclusion criteria, and same laser apparatus.

Although this study did not show better clinical outcomes of reduced fluence PDT in treating chronic CSC compared to half-dose PDT, reduced fluence PDT has a number of advantages. These include convenience in preparation and a relatively stable retinal verteporfin concentration needed to simultaneously treat 2 distant leak points or both eyes. Thus, we suggest reduced fluence PDT as an alternative strategy for treating CSC.

Conflicts of Interest

The authors have no financial interest in any aspect of this article.

References

1. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. *Am J Ophthalmol* 1967;63(3 Suppl):1-139.
2. Levine R, Brucker AJ, Robinson F. Long-term follow-up of idiopathic central serous chorioretinopathy by fluorescein angiography. *Ophthalmology* 1989;96:854-9.
3. Yannuzzi LA. Type-A behavior and central serous chorioretinopathy. *Retina* 1987;7:111-31.
4. Robertson DM. Argon laser photocoagulation treatment in central serous chorioretinopathy. *Ophthalmology* 1986;93:972-4.
5. Cardillo Piccolino F, Eandi CM, Ventre L, et al. Photodynamic therapy for chronic central serous chorioretinopathy. *Retina* 2003;23:752-63.
6. Costa RA, Scapucin L, Moraes NS, et al. Indocyanine green-mediated photothrombosis as a new technique of treatment for persistent central serous chorioretinopathy. *Curr Eye Res* 2002;25:287-97.
7. Yannuzzi LA, Slakter JS, Gross NE, et al. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. *Retina* 2003;23:288-98.
8. Chan WM, Lam DS, Lai TY, et al. Choroidal vascular remodeling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. *Br J Ophthalmol* 2003;87:1453-8.
9. Lai TY, Chan WM, Lam DS. Transient reduction in retinal function revealed by multifocal electroretinogram after photodynamic therapy. *Am J Ophthalmol* 2004;137:826-33.
10. Chan WM, Lai TY, Lai RY, et al. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. *Ophthalmology* 2008;115:1756-65.
11. Chan WM, Lai TY, Lai RY, et al. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy: one-year results of a prospective study. *Retina* 2008;28:85-93.
12. Reibaldi M, Boscia F, Avitabile T, et al. Low-fluence photodynamic therapy in longstanding chronic central serous chorioretinopathy with foveal and gravitational atrophy. *Eur J Ophthalmol* 2009;19:154-8.
13. Reibaldi M, Cardascia N, Longo A, et al. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. *Am J Ophthalmol* 2010;149:307-15.e12.
14. Rouvas A, Stavrakas P, Theodossiadis PG, et al. Long-term results of half-fluence photodynamic therapy for chronic central serous chorioretinopathy. *Eur J Ophthalmol* 2012;22:417-22.
15. Rouvas AA, Papakostas TD, Ntouraki A, et al. Photodynamic therapy, ranibizumab, and ranibizumab with photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Retina* 2011;31:464-74.
16. Shinojima A, Kawamura A, Mori R, et al. Detection of morphologic alterations by spectral-domain optical coherence tomography before and after half-dose verteporfin photodynamic therapy in chronic central serous chorioretinopathy. *Retina* 2011;31:1912-20.
17. Maruko I, Iida T, Sugano Y, et al. One-year choroidal thickness results after photodynamic therapy for central serous chorioretinopathy. *Retina* 2011;31:1921-7.