Comparison of Visual and Anatomical Outcomes of Half Fluence - Full Dose and Half Dose - Full Fluence Photodynamic Therapy in Eyes with Chronic Central Serous Chorioretinopathy

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ABSTRACT

Purpose: To compare half fluence-full dose and half dose- full fluence photodynamic therapy (PDT) regarding visual acuity and anatomic changes in chronic central serous chorioretinopathy (CSCR).

Materials and Methods: We retrospectively reviewed 60 patients with chronic CSCR patients who underwent half fluence- full dose (group 1, 30 patients) or half dose- full fluence (group 2, 30 patients). The best corrected visual acuity (BCVA), central macular thickness (CMT), subfoveal choroidal thickness (SFCT), serous retinal detachment (SRD) and retina pigment epithelial detachment (PED) were compared between the groups at baseline, on months 1, 3, 6 and 12 during follow-up.

Results: The mean follow-up duration was 12 months in both groups. The mean number of repeated PDTs following first PDT was 0.48 ± 0.20 (range, 0-2) in the group 1 and 1.09 ± 0.80 (range, 0-3) in the group 2 during 12-months follow-up (p = 0.031). In Group 1, BCVA was increased from 0.69 ± 0.28 logMAR (logarithm of the Minimum Angle of Resolution) at baseline to 0.20 ± 0.18 logMAR on month 12 (p <0.001). The CMT was decreased from 380.26 ± 104.77 µm at baseline to 267.86 ± 73.95 on month 12 (p <0.001). The SFCT was decreased from 274.60 ± 38.53 µm at baseline to 236.10 ± 37.09 µm on month 12 (p = 0.002) while SRD showed a statistically significant decrease during follow-up when compared to the baseline (p <0.001). In group 2, the BCVA was increased from 0.66 ± 0.33 logMAR at baseline to 0.17 ± 0.16 logMAR on month 12 (p <0.001). CMT was decreased from 355.93 ± 101.74 µm at baseline to 258.03 ± 66.28 µm on month 12 (p <0.001). SFCT was decreased from 274.40 ± 16.06 µm at baseline to 254.50 ± 28.12 µm on month 12 (p<0.001) while SRD showed a statistically significant decrease during follow-up compared to the baseline (p <0.001). On month 12, there was no statistically difference between the groups regarding SRD (p=0.752). In both groups, no statistically significant change was observed in PED during the follow-up when compared to the baseline (p> 0.05). In the study, number of PDTs were increased by decreasing doses administered in PDT (r = -0.339, p = 0.008). In both groups, no PDT-related complication was observed.

Conclusion: Both half fluence-full dose and half dose-full fluence PDT were effective in the treatment of chronic CSCR. No significant difference was observed in visual or anatomical outcomes between groups. Although no systemic complications developed depending on the PDT dose, the number of relapses increased by reducing amount of doses. amount decreased. Based on these results, we observed that the number of PDT relapses can be related to the dose amount.

Keywords: Chronic central serous chorioretinopathy, Photodynamic therapy, Optical coherence tomography.

INTRODUCTON

Central serous chorioretinopathy (CSCR) is a chorioretinal disease characterized by serous retinal detachment at posterior pole and/or pigment epithelium detachment (PDE). The main findings include reduction in visual acuity, micropsy, metamorphopsia and central scotoma. Frequently, it is more commonly seen in men than women among younger adults and it is often unilateral. An association with type personality disorder and history of stress has been identified.[1]

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Fundus fluorescein angiography (FFA) is a useful imaging modality to distinguish CSCR from other disorders from choroidal neovascularization (CNV) in atypical CSCR. The FFA is used to determine leakage areas when focal argon laser therapy is considered in CSCR. In early phase, the characteristic FFA finding was solitary hyper-fluorescent point representing dye leakage from choroid along with retinal pigment epithelium (RPE). In minority of patients, leakage area is extended with no punctate origin. The punctate leakage was observed within area of 1500 mm and often at superiornasal region.[2] Typically, fluorescein dye spreads evenly in all direction to stain and demarcate margins of neurosensory detachment. The classical "smokestack" sign is seen less commonly (7-20%).[3-5] The ink blot or mushroom-shaped staining patterns are more common. The previous CSCR and chronic neurosensory detachment result in "fenestration defect" areas due to multi-focal RPE atrophy and gravity.[6]

As demonstrated by indocyanine green angiography (IGA), the increased permeability of choroidal vessels as a result of fluid accumulation among retinal layers seems as pathophysiology of CSCR.[1,7,8] Gass proposed that increased permeability of choriocapillaris can lead CSCR.[9] In the studies by Iida et al.[10] and Spaidae et al.[11] reported that there was increased choroidal vascular permeability in majority of symptomatic eyes. In chronic CSCR, persistent SRD and subsequent RPE dysfunction as well as atrophic and/or degenerative RPE changes are observed. It is accepted that this results in loss of vision [9].

Optical coherence tomography (OCT) can measure choroidal thickness; however, no method other than IGA can visualize choroidal changes in vivo. Spaide et al. reported that enhanced-depth OCT can visualize choroid.[11]

Verteporfin, a benzoporphyrin derivative, is approved in chorioretinal disorders due to its high affinity to RPE. Verteporfin exerts its effects by binding low-density lipoproteins in the plasma.[12] The photodynamic therapy (PDT) triggers formation of free radicals in choriocapillaris; as a result, injury and hypo-perfusion develop in vascular endothelial cells, leading neovascularization in the choriocapillaris beneath injured RPE.[13] In recent years, choroidal vascular permeability was decreased; as a result, RPE leakage was regressed following standard PDT or half-dose PDT in CSCR.[14-18] Maruko et al. reported that the subfoveal thickness was decreased within a month after half-dose PDT with verteporfin but long-term outcomes are unknown.[19]

Alkin et al. demonstrated that both half-dose and half-fluence PDT were equally effective regarding resolution of subretinal fluid (SRF) and visual acuity improvement.[20] Kim et al. showed that there was ellipsoid zone recovery on month 12 in 73% and 54% of eyes treated with half-fluence and half-dose PDT, respectively.[21] However, both studies evaluated only visual acuity, central foveal thickness and SRF resolution at relatively short follow-up.

In this study, we aimed to determine relationship between anatomical and visual changes and dose and fluence variation in PDT used to treat chronic CSCR.

MATERIAL AND METHOD

In the study, we retrospectively reviewed files of 60 patients with chronic CSCR including 30 patients underwent full dose-half fluence PDT (group 1)and 30 patients received half dose-full fluence PDT (group 2) in a tertiary center between June, 2015 and March, 2020. The study was conducted in accordance to tenets of Helsinki Declaration. The study approved by Ethics Committee on Clinical Research (approval#2020-02; approval date: 20.01.2020). All patients gave written informed consent..

The central serous chorioretinopathy often manifests in classical and chronic forms. The classical CSCR is defined presence of SRD due to isolated leakage points while chronic CSCR is defined as persistent SRD for 6 months and/or diffuse areas of leakage from extended areas of RPE injury.[22]

The patients having history of previous treatments with intravitreal anti-VGEF injection, laser photocoagulation and long-term ophthalmic drops were excluded. In addition, patients with chorioretinal diseases that may cause SRD, SRF and secondary macular edema; ischemic maculopathy; Irwin-Gass syndrome; age-related exudative macular degeneration; diabetic retinopathy; uveitis; and other vitreoretinal disorders; patients with history of intraocular surgery other than cataract surgery, patients with other conditions that may trigger visual impairment and those attending follow-up visits irregularly were also excluded.

Among clinical examination and imaging modalities, best-corrected visual acuity (BCVA) measurement, slit lamp examination with contact lens or non-contact lens, indirect ophthalmoscopy, digital FFA and IGA were used for diagnosis of central serous chorioretinopathy. The BCVA was measured using Snellen charts and transformed into logMAR digits (Logarithm of Minimum Angle of Resolution) for statistical purposes. All eyes were examined using Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). The CSCR was diagnosed by FFA and IGA evaluations in the presence of SRF that may affect macula related to idiopathic leakages from RPE. The areas of choroidal vascular hyper-permeability were observed as

hyper-fluorescent in mid-phase IGA images.

Due to diurnal variation in choroidal thickness, all examinations were performed between 8:30 and 12:00. Horizontal and vertical linear scanning over fovea were performed for subfoveal choroidal thickness (SFCT) defined as distance between base of subfoveal RPE and margin of chorido-scleral interface. Choroid was visualized using enhanced-depth mode of Spectralis OCT device. The eye scanning system was used in each session and average of 100 scanning was used to improve signal: noise ratio. No additional equipment or software is required for OCT in Heidelberg Spectralis OCT. For SFCT, OCT data were measured at vertical and horizontal sections which were averaged.

The patients were informed regarding risks and benefits of PDT in patients with leakage in foveal avascular region and SRF and PDT was performed in patients accepted. These patients were included to the study. The patients with chronic CSCR were treated with PDT as first-line treatment. For PDT procedure, 689 nm laser system (Carl Zeiss, Dublin, CA, USA) with contact lens (Volk Area Centralis®).

PDT protocol:

1) In full dose group, one fluence PDT was given by modified total light energy (25 J/cm^2) and laser intensity (300 mW/cm^2) at standard verteporfin dose (6 mg/m^2) and standard duration (83 seconds) for laser emission.

2) In half dose group, one fluence PDT was given by increased total light energy (50 J/cm^2) and laser intensity (600 mW/cm^2) at verteporfin dose of 3 mg/m^2 and duration of 146 seconds for laser emission.[23]

Whole lesion area was determined by measuring largest linear size of abnormal choroidal vascular area using the software on IGA. The PDT area was calculated as adding 1 mm to diameter of lesion. All patients were given eye protection after PDT and instructed to avoid powerful light.

Criteria for PDT repetition:

1) Recurrent SRF within first month after PDT persisting for at least 2 months

2) Lack of improvement or worsening in BCVA due to changes of central macula and SRF after PDT

3) No regression in SRF and SRF during follow-up visits every 3 months

Subfoveal choroidal thickness, central macular thickness (CMT), SRD height and presence of PED were assessed the day before PDT and on months 1, 3, 6 and 12 after PDT using enhanced-dept OCT imaging and Spectralis OCT. Figure 1 presents OCT and IGA images in a patient received full dose-half fluence.

Visual acuity, SRD and PED were assessed in all examinations and number of recurrences and PDT repetitions were recorded at 12-months follow-up period.

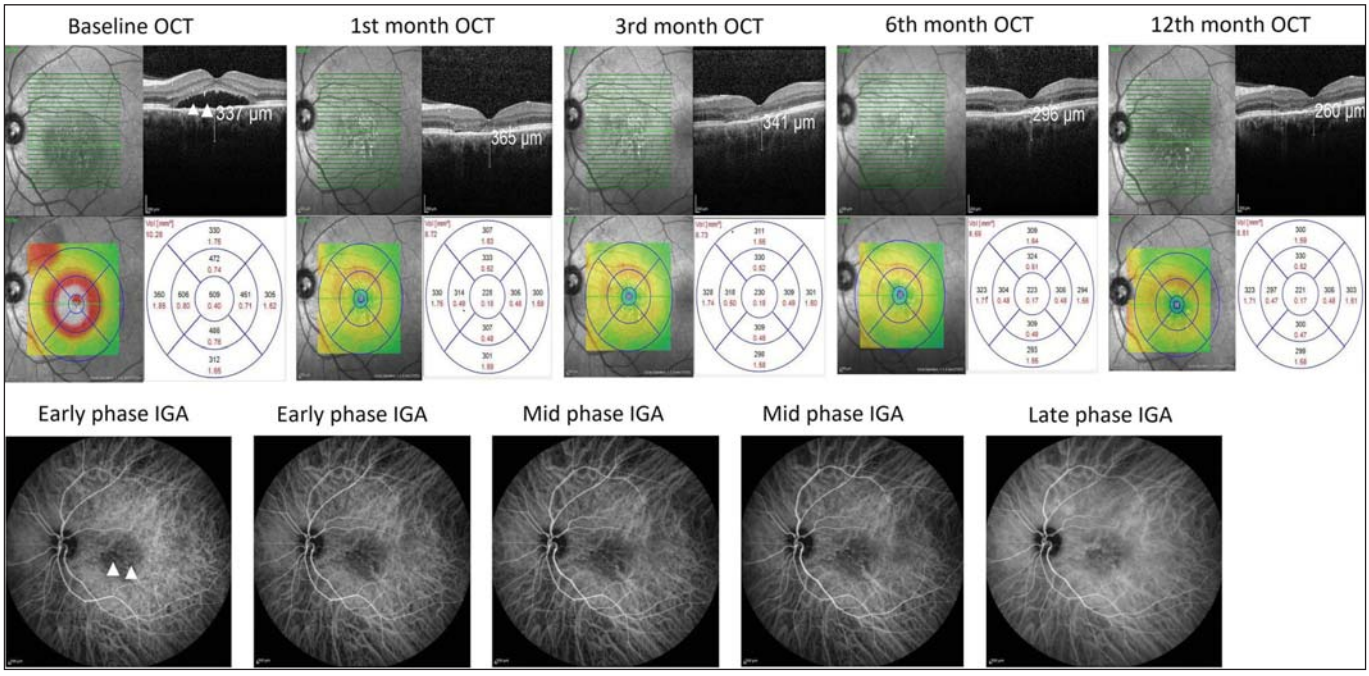

Figure 1: *Optical coherence tomography (OCT) and indocyanine green angiography (IGA) images of a patient underwent full dose-half fluence PDT.*

Statistical analysis

Kolmogorov-Simirnov and Shaphiro Wilk tests were used to assess normal distribution in continuous variables. Mean ± standard deviation was used in parametric tests while median (min-max) values were used in non-parametric tests. Categorical variables are presented as frequency and percent. The BCVA values were transformed into logMAR digits (Logarithm of Minimum Angle of Resolution) for statistical purposes. The BCVA and anatomical changes before and after PDT were compared using Friedman test and post-hoc Dunn test. Mann Whitney U test was used to compare number of recurrent PDTs between groups. For analysis of number of PDT and doses between groups, Pearson's and Spearman's rank correlation coefficients were used where appropriate. A p value<0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS version 22.0 (Statistical Package for Social Sciences).

FINDINGS

There were 50 men (83%) and 10 women (17%) in the study population. Mean age was 44.76 ± 5.77 years (range, 27-55 years). Of the eyes included 22 were right eye (36%) and 38 eyes (64%). The follow-up duration was 12 months.

There were 25 men (83%) and 5 women (17%) and Mean age was 43.93 ± 6.40 years (range, 27-54 years) in group 1 whereas There were 25 men (83%) and 5 women (17%) and Mean age was 45.60 ± 5.04 years (range, 36-55 years) in group 2.

There was no significant difference in age, baseline BCVA, CMT, PED, SRF and SFCT between groups (p=0.618, p=0.250, p=0.355, p=0.139, p=0.636, p=0.660). No significant changes were observed in intraocular pressure (IOP) before and after treatment.

Table 1 presents clinical and demographic characteristics of patients.

Group 1 (full dose-half fluence); Mean number of PDT repetitions was 0.48 ± 0.20 (range, 0 to 2). The mean **BCVA** was found as 0.69 ± 0.28 log MAR at baseline, 0.34 ± 0.17 log MAR on month 1, 0.35 ± 0.25 log MAR on month 3, 0.32 ± 0.29 log MAR on month 6, 0.20 ± 0.18 log MAR on month 12 (p<0.001). The mean **CMT** was 380.26 ± 104.77 µm at baseline, 277.76 ± 82.85 µm on month 1, 273.13 ± 84.17 µm on month 3, 275.86 ± 80.45 µm on month 6 and 267.86 ± 73.95 µm on month 12 (p<0.001). The mean **SFCT** was 274.60 ± 38.53 µm at baseline, 236.26 ± 38.65 µm on month 1, 235.93 ± 35.22 µm on month 3, 234.16 ± 34.87 µm on month 6 and 236.10 ± 37.09 µm on month 12 (p=0.002). The **SRD** showed significant reduction at follow-up when compared to baseline (p<0.001). No significant difference was detected in **PED** at follow-up period when compared to baseline (p=0.343).

Group 2 (half dose-full fluence); Mean number of PDT repetitions was 1.09 ± 0.80 (range, 0 to 3). The mean **BCVA** was 0.66 ± 0.33 log MAR at baseline, 0.30 ± 0.20 log MAR on month 1, 0.30 ± 0.28 log MAR on month 3, 0.24 ± 0.23 log MAR on month 6 and 0.17 ± 0.16 log MAR on month 12 (p<0.001). The mean **CMT** was 355.93 ± 101.74 µm at baseline, 266.73 ± 63.98 µm on month 1, 275.30 ± 90.02 µm on month 3, 260.50 ± 74.11 µm on month 6 and 258.03 ± 66.28 µm on month 12 (p<0.001). The mean **SFCT** was 274.40 ± 16.06 µm at baseline, 272.26 ± 30.32 µm on month 1, 273.60 ± 27.60 µm on month 3, 275.23 ± 29.82 µm on month 6 and 254.50 ± 28.12 µm on month 12 (p<0.001 The **SRD** showed significant reduction at follow-up when compared to baseline (p<0.001). No significant difference was detected in **PED** at follow-up period when compared to baseline (p=0.329).

In the study, number of PDTs were increased by decreasing doses administered in PDT (r = -0.339, p = 0.008). In both groups, no PDT-related intraocular or systemic complication was observed.

Table 1: *Clinical and demographic characteristics of patients.*

PDT type	**Group 1**	**Group 2**	**p value**
	Full dose	**Half dose**	
Eye	**30**	**30**	
Gender	**5^{f} 25^{m}**	**5^{f} 25^{m}**	
Age (mean ±SD, years)	**43.93 ± 6.40**	**45.60 ± 5.04**	**0.351**
Side	**13^{r} 17^{l}**	**10^{r} 20^{l}**	
Number of PDT repetitions (mean ±SD)	**0.48 ± 0.20**	**1.09 ± 0.80**	***0.031****
Number of PDT repetitions (distribution)	**0 ile 2**	**0 ile 3**	
SRD at final visit (+/-)	**(10/20)**	**(12/18)**	**0.752**

PDT, photodynamic therapy; SD, standard deviation; ^{f} female, ^{m} male; ^{r} right, ^{l} left; SRD, serous retina detachment; *Mann Whitey U test

Figure 2 presents BCVA, CMT, SFCT and number of PDTs. Table 2 presents BCVA, CMT, SFCT, SRF and PED results at baseline and follow-up.

DISCUSSION

In the study, similar results were observed regarding anatomic and visual success in both groups. However, greater number of PDT was required to achieve similar effect in the group 2.

Central serous chorioretinopathy is a chorioretinal disease characterized by self-limiting, localized neurosensory retinal detachment which commonly seen at macular region and/or PED.[7]

In current clinical practice, PDT is one of the treatment options in CSCR. PDT is an approach tailored treatment of disease with choroidal hyper-permeability. In chronic CSCR, therapeutic effect of PDT is attributed choriocapillaris occlusion, leading subsequent decrease in choroidal hyper-permeability and increased absorption of subretinal fluid.[24,25] It was shown that PDT is associated with improved vision and decreased SRF in CSCR [26]. It was reported that half dose PDT is more than or as effective as full dose, half fluence and half time PDT regimens in both acute and chronic CSCR. The PDT has several adverse effects including reduction in vision, headache, severe eye redness, pain and glare of eyes, chest pain, flushing, dry eye, constipation, diarrhea, muscular and articular pain,

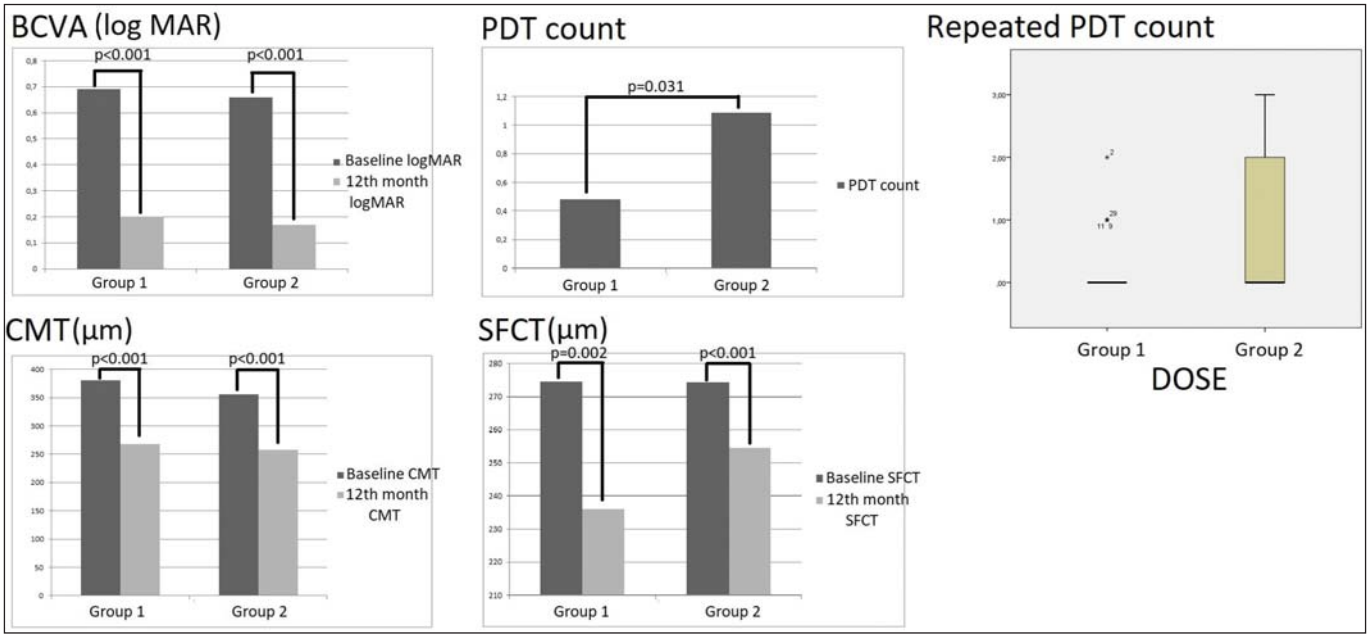

Figure 2: *Results of BCVA, CMT, SFCT and number of PDTs are presented in the graphic.*

Table 2: *Mean best-corrected visual acuity (BCVA), central macular thickness (CMT), subfoveal choroidal thickness (SFCT) serous retinal detachment (SRD) and retinal pigment detachment (PED) values at baseline and during follow-up.*

Groups		Baseline	1st month	3rd month	6th month	12th month	p value*
Group 1	BCVA (log MAR)	0.69±0.28	0.34±0.17	0.35±0.25	0.32±0.29	0.20±0.18	<0.001*
Full dose	CMT (µm)	380.26±104.77	277.76±82.85	273.13±84.17	275.86±80.45	267.86±73.95	<0.001*
Half fluence	SFCT (µm)	274.60±38.53	236.26±38.65	235.93±35.22	234.16±34.87	236.10±37.09	0.002*
	SRD (+/-)	(30/0)	(16/14)	(12/18)	(12/18)	(10/20)	<0.001*
	PED (+/-)	(10/20)	(8/22)	(7/23)	(8/22)	(10/20)	0.343
Group 2	BCVA (log MAR)	0.66±0.33	0.30±0.20	0.30±0.28	0.24±0.23	0.17±0.16	<0.001*
Half dose	CMT (µm)	355.93±101.74	266.73±63.98	275.30±90.02	260.50±74.11	258.03±66.28	<0.001*
Full fluence	SFCT (µm)	274.40±16.06	272.26±30.32	273.60±27.60	275.23±29.82	254.50±28.12	<0.001*
	SRD (+/-)	(30/0)	(18/12)	(17/13)	(13/17)	(12/18)	<0.001*
	PED (+/-)	(5/25)	(4/26)	(6/24)	(2/28)	(4/26)	0.329

*Friedman test; BCVA: best-corrected visual acuity; CMT: central macular thickness; SFCT: central foveal choroidal thickness; SRD: serous retinal detachment; PED: pigment epithelium detachment.

fever and vomiting. In some centers, PDT dose reduction was employed to decrease such systemic adverse effects.[27] In our study, no systemic or ocular adverse effect and/or complication was observed in our study.

In a study by Nicolo et al. it was reported that half dose PDT provided rapid anatomic improvement than half fluence PDT and that complete SRF resolution was achieved in 86% and 61% at month 1 in patients with chronic CSCR.[28]

In other studies, it was found that half fluence PDT was as effective as full fluence PDT in the treatment of chronic CSCR[29] and that half dose PDT was as effective as full dose PDT in permanent treatment[30] In addition, results were comparable regarding efficacy in half time and half dose PDT.[31,32]

In a retrospective case series, Liu et al. compared half dose PDT with full fluence PDT and half fluence PDT and found complete SRF resolution in 93% and 64% of cases, respectively, indicating significant difference ($p<0.001$).[33]

In a retrospective study on 42 eyes by Park et al., full dose (verteporfin, 6 mg/m^2), half dose (verteporfin, 3 mg/m^2) and half dose-half fluence PDT (verteporfin, 3 mg/m^2 and energy, 25 J/cm^2) were given to patients. The BCVA, SFCT, SRF height and choroidal vascular index were assessed at baseline and on month 3 after PDT. A significant improvement in BCVA and reduction SRF height were detected in full dose and half doe PDT group; however, no significant difference was detected in BCVA and SRF height in half dose-half fluence group. Although authors found that full dose and half dose PDT were effective in chronic CSCR, they advocated that half dose could reduce complications of PDT. No significant difference was detected in half dose-half fluence group.[34]

In a study, Kim et al. assigned 52 eyes of 52 patients with chronic CSCR into 2 groups: half fluence PDT (26 eyes) and half dose PDT (26 eyes). The BCVA was significantly improved while CMT and SFCT were significantly decreased in both groups. Authors defined ellipsoid zone continuity as photoreceptor recovery and assessed as presence of visible interdigitation zone; they found photoreceptor recovery in 19 eyes (73%) in half fluence group and 14 eyes (54%) in half dose group on month 12 ($p=0.150$). No significant difference was detected in photoreceptor recovery between groups ($p=0.301$). Delayed photoreceptor recovery (>12 months) was correlated with impaired external limiting membrane at baseline ($p=0.019$), disease duration ($p=0.005$) and PDT-foveal center distance (100 µm unit, $p=0.027$). However, delayed photoreceptor recovery (>12 months) had no correlation with PDT modality. Authors showed no significant difference in anatomic and visual outcomes of chronic CSCR patients between half fluence and half dose PDT groups .[21]

In a study by Maruko et al., half dose PDT (over one year) was given to 13 eyes of 13 patients with chronic CSCR and the SFCT was measured using enhanced-depth OCT. Mean SFCT was decreased from 397 ± 108 µm at baseline to 323 ± 120 µm on month 1, 312 ± 117 µm on month 3, 317 ± 117 µm on month 6 and 321 ± 122 µm on month 12 ($p=0.001$).The SFCT was significantly increased to 441 ± 120 µm at the end of day 2 ($p=0.01$). No recurrence was detected. In conclusion, authors observed reduction in SFCT values, reduced choroidal vascular permeability at the end of month 1 and prolonged remission up to 12 months.[35]

Sheptulin et al. aimed to assess efficacy of half fluence PDT in patients with chronic CSCR. In the retrospective study, PDT with a protocol of full dose (6 mg/m^2)-half fluence (43second) was given to 114 eyes of 113 patients with chronic CSCR and SRF resolution, recurrence and pretreatment and post-treatment BCVA were assessed. Authors found that PDT showed 80% (91 eyes) on month 6 and 87% (99 eyes (on month 12) with unresponsiveness rate of 13%). Complete SRF resolution was observed at week 8 in average and a significant improvement was observed in BCVA ($p<0.001$). Authors concluded that half dose PDT is effective regarding anatomic and visual outcomes in chronic CSCR.[36] However, number of PDT repetition and mean number of PDTs were not specified in the study.

On baseline OCT, presence of PED has been proposed as a prognostic factor for SRF resolution and worse visual outcome after half dose PDT with verteporfin. Based on these findings, it was proposed that PDT is effective in chronic CSCR without PED.[27, 37] However, in our study, no significant difference was detected regarding effects on efficacy and prognosis despite higher rate of baseline PED in full dose-half fluence group when compared to half dose-full fluence group. Subfoveal exudation, thickened choroid and flat, irregular PED on OCT scanning, well-defined plaque on IGA and RPE atrophy and diffuse neurosensory detachment related to scattered RPE areas are diagnostic for CNVM secondary to CSCR.[38] In our study, half fluence-full dose PDT regimen under IGA guidance seems to be promising regarding safety profile since no secondary CNV or RPE atrophy was observed. No loss of vision or adverse event was observed either immediately after PDT or during follow-up.

In majority of above-mentioned studies, it was shown that half dose and half fluence PDT is at least as effective as full

dose PDT and has advantages (systemic adverse effects of verteporfin). In our study, no significant difference was detected in efficacy between half dose and full dose PDT. However, number of PDT repetitions was lower in full dose PDT group. This translated as longer duration of action and higher efficacy in full dose group. In our study, the CMT and SFCT were significantly decreased while the BCVA was significantly improved in both groups. In addition, we observed prolongation in duration of action with decreased number of recurrences by increased dose. Our study has some advantages including regular follow-up periods and detailed statistical data such as mean number of PDT. The disadvantages include relatively small sample size and retrospective design.

In conclusion, no significant difference was detected in PDT efficacy regarding anatomic and visual outcomes between groups. Number of PDT repetitions was significantly lower in full dose group when compared to half dose group. Although systemic complications were develop depending on PDT dose, an increase was detected in number of recurrences by reduction of dose. No systemic or ocular adverse effect and/or complication were detected in our study. Based on the results, we concluded that number of PDT recurrences might be associated with dosage.

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