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Original Article/นิพนธ์ต้นฉบับ

Choroidal Vascularity Index Changes after Treatment of Persistent Central Serous Chorioretinopathy with either Spironolactone or Half-Dose Photodynamic Therapy

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Abstract

Purpose: To evaluate choroidal vascularity index (CVI) changes after treatment with either spironolactone or half-dose photodynamic therapy (PDT).

Design: Retrospective study

Methods: We enrolled 34 patients with subretinal fluid accumulation persisting for more than 3 months due to central serous chorioretinopathy (CSC); 16 patients were treated with spironolactone and 18 with PDT. We reviewed the central OCT-B scans at baseline and 1 and 3 months after treatment. We defined the CVI as the percent of vascular/luminal pixels over the total number of pixels and compared the results between the treatment groups.

Results: The baseline CVIs were 60.33% in the spironolactone treatment group and 60.51% in the PDT group. After treatment, the CVI remained similar in the spironolactone group, but it increased significantly one month (63.35%) and three months (63.56%, $P = 0.004$, 0.001) after the PDT. The total and luminal choroidal areas were both decreased after PDT, but only the stromal area was significantly decreased at one and three months ($P = 0.001$and $P < 0.001$, respectively). By month three, the subfoveal choroidal thickness (SFCT) had decreased by 30.32 μm ($P = 0.013$) in the PDT group and by 18.88 μm ($P = 0.195$) in the spironolactone group.

Conclusion: After CSC treatment, the choroid remained virtually unchanged following the spironolactone therapy, whereas the choroidal thickness was significantly reduced and the CVI increased following PDT. These anatomic changes in the choroid following PDT may explain why the effects of PDT are more durable and potent than those of spironolactone for CSC.

Keywords: central serous chorioretinopathy (CSC), choroidal vascularity index (CVI), choroidal thickness (CT), choroidal vasculature, spironolactone, half-dosed photodynamic therapy

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Introduction

Central serous chorioretinopathy (CSC) is a pachychoroid spectrum disorder[1-4] characterized by choroidal abnormalities including increased choroidal thickness, large dilated outer choroidal vessels that may compress the inner choroid[4], and choroidal vascular hyperpermeability[5-7] (best detected via indocyanine green angiography imaging)[8-10]. Subretinal fluid accumulation may occur during periods of activity and persisting fluid can lead to vision loss.

The etiology and pathogenesis of CSC remain unclear; however, corticosteroids (exogenous or endogenous) seem to aggravate the condition[11-15]; and, over- or inappropriate activation of the mineralocorticoid receptor (MR)[7] may lead to choroidal vascular dilatation and hyperpermeability. MR activation may also promote muscle cell fibrosis via activation of the placental growth factor (PGF)/VEGF receptor 1 (VEGFR1) pathway, and MR antagonists may prevent pathologic vascular remodeling[16]. Zhao and colleagues found mineralocorticoid receptors in ganglion, cells of inner nuclear layer, and Muller cells in rats eyes[17]. Spironolactone is a well-established MR antagonist used to treat hypertension and congestive heart failure, and it has been suggested as a potential oral treatment for non-resolving CSC[18-24]. Small studies have reported potential treatment efficacies in patients with chronic CSC[18-23] as well as faster absorption of subretinal fluid in cases of acute CSC[24]. Lee and colleagues found similar short-term efficacies of best-corrected visual acuity improvement and decrease of subretinal fluid height for both oral spironolactone and half-dose photodynamic therapy[23], but only patients in the PDT group decreased their subfoveal choroidal thickness after the treatment. Whether the choroidal thickness changes following MR antagonist treatment remains a controversial point[17,19-21]. Eplerenone is another MR antagonist that may be preferable for male patients with CSC because it is less probable to induce hormonal issues like gynecomastia. However, eplerenone's MR antagonist effect is considerably less potent than spironolactone's. Moreover, eplerenone failed to demonstrate a significant treatment benefit in eyes with CSC in a randomized clinical trial[25].

Photodynamic therapy (PDT) has been well-studied and is commonly accepted as an effective treatment for chronic CSC[26-29]. PDT is typically applied using either half-dose (of verteporfin) or half-fluence (of light) regimens. PDT's effects are thought to be due to a reduction in choroidal hyperpermeability[29] through transient occlusion of choriocapillaris, a histopathological finding demonstrated in human eyes[30]. This inner choroidal occlusion is also responsible for the subsequent decrease in choroidal thickness and choroidal vascular dilatation[31-32].

The choroidal vascularity index (CVI) is a metric developed to specifically assess the relative proportions of the vasculature and stroma in the choroid[33-39], the index is valuable for assessing the status of various diseases, providing information not captured by measurements of choroidal thickness alone. The CVI is computed as the ratio of the luminal area (LA) divided by the total choroidal area (TCA). A difference in CVI suggests a difference in the proportion of vessels relative to that in the stroma. The CVI in eyes with active CSC has been shown to be higher than that in the fellow eyes when compared to those in age-matched controls[34]. Kinoshita and colleagues reported that both the hyperreflective area(stromal structure) of the inner choroid and the hyporeflective area(luminal structure) of the outer choroid are decreased significantly after half-dose PDT in patients with CSC[40]. However, to the best of our knowledge, no studies have assessed the impact of oral spironolactone on the CVI. Thus, we designed this study to evaluate the CVI changes over time following oral spironolactone in both the affected CSC eye and the fellow eye, and we compared the effects to those after half-dose PDT.

Methods

For this retrospective study, we identified and reviewed the records of 34 consecutive patients who were newly diagnosed and recurrent CSC with persistent subretinal fluid for more than 3 months at the Mettapracharak Hospital between 2013 and 2018. Among these patients, 16 (16 eyes) received 50 mg per day of oral spironolactone (Aldactone; Pfizer, New York, NY) for 30 days and 18 patients (18 eyes) were treated with half-dose PDT (HD-PDT). Our inclusion criteria included: (1) age between 18 years old and above; and, (2) best-corrected visual acuity (BCVA) between 20/200 and 20/30. Both unilateral and bilateral CSC were included in the study. We excluded records of patients with any of the following criteria: any evidence of other macular disease or a complicating feature such as choroidal neovascularization, polypoidal choroidal vasculopathy, or diabetic macular edema; and, pregnant patients. The Medical Ethics Committee of Mettapracharak Hospital approved the research protocols, the number of approval was COA011/2563, and we conducted the research adhering to the tenets set forth in the Declaration of Helsinki.

The patients in the PDT group had all undergone fluorescein angiography (FA) (HRA-2; Heidelberg Retina Angiograph System, Heidelberg Engineering, Heidelberg, Germany) to identify the leakage region (fluid on OCT) and to calculate the treatment spot size (defined as the smallest circular region able to completely cover the region of leakage on the FA). After obtaining informed consents, 3 mg/m^2 of verteporfin (Visudyne; Novartis AG, Bulach, Switzerland) were infused in the antecuboidal vein during a period of 10 minutes; subsequently, 5 minutes after the infusion, the leakage area was treated with 683 nm of light for a period of 83 seconds, with a total irradiation of 50 J/cm^2. Following the PDT, patients were advised to avoid bright lights or sunlight for at least 24 hours.

The records of all patients also included data on duration of symptoms(months), defined as the recognition of disturbance of visual function, including visual acuity, color vision and contrast sensitivity[5] and a complete ophthalmic examination including BCVA, slit-lamp biomicroscopy, dilated ophthalmoscopy, and spectral domain optical coherence tomography (OCT) with enhanced-depth imaging (EDI) OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) at baseline just prior to treatment, and again 1 and 3 months after treatment. The main outcome endpoints for our study were the change in CVI and the subfoveal choroidal thickness (SFCT) 1 and 3 months after the start of treatment (PDT or spironolactone).

To facilitate evaluation of the choroid, the spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) scans were acquired using the EDI technique. A 30 × 15 degrees (8.8 × 4.4 mm) pattern centered on the fovea was scanned consisting of 19 B-scans with a spacing of 238 μm between scans. Each B-scan was averaged 9 to 11 times. The central B-scan was used to measure the choroidal thickness and CVI. The subfoveal choroidal thickness (SFCT) was manually measured from the retinal pigment epithelium (RPE) outer surface to the inner scleral surface using the caliper tool in the Heidelberg Eye Explorer Software (Version 1.10.4.0). We defined the central subfield thickness (CST) as the average thickness of the macula in the 1-mm central region of the Early Treatment of Diabetic Retinopathy Study (ETDRS) grid, and we measured it from the internal limiting membrane to the RPE; therefore, it included both the intraretinal thickening and subretinal fluid.

Choroidal Vascularity Index (CVI) Computation

We selected the central EDI-OCT B-scan for binarization using the publicly-available Image J software (Fiji; http://fiji.sc/Fiji). We computed the binarization protocol from Agrawal and colleagues[35]. First, we selected the region of interest (ROI) as a zone

on the foveal center with a width of 1,500 μm (750 μm to the nasal and temporal sides of the fovea). We placed the inner border of the ROI at the outer RPE and the outer border at the choroid-sclera interface. The images were adjusted to 8 bits, and we applied the Niblack autolocal threshold method (Figure 1) to differentiate pixels into bright and dark ones. We counted dark pixels as belonging to the LA corresponding to the vascular lumens. The remaining bright pixels were deemed to represent the choroidal stroma. Before the computation, we compared the binarized image with the original structural OCT image to confirm that the binarized image accurately reflected the vascular and stromal components visible on the original OCT image. The total number of pixels in the ROI served as the denominator for CVI computations. We defined the CVI as the ratio of the LA divided by the total area. An experienced, certified Doheny Image Reading Center (DIRC) grader (WT) performed all gradings and the CVI analyses.

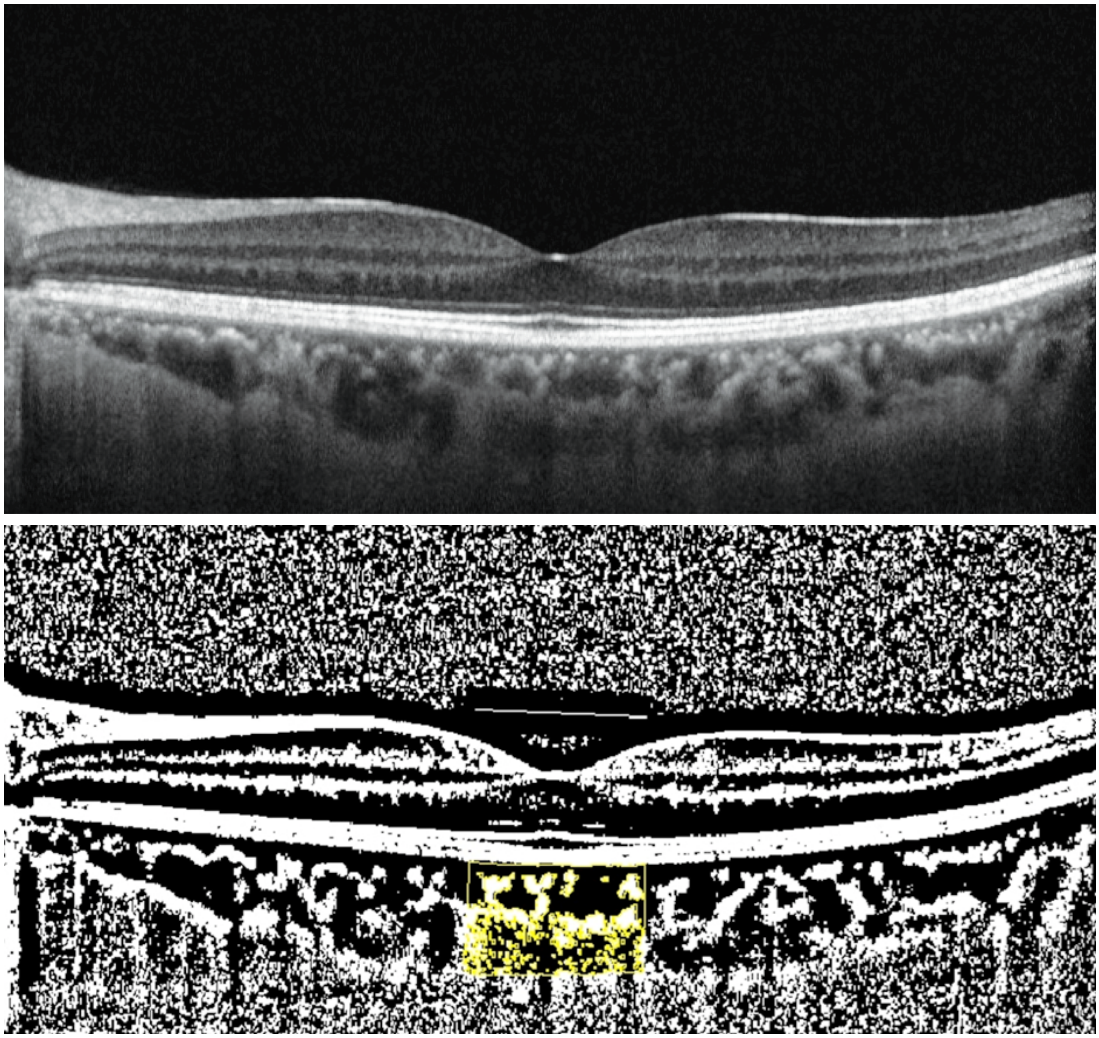

Figure 1 Enhanced-depth optical coherence tomography central B-scan of the left eye (left panel). Following binarization, the choroid was divided into dark (vascular lumen) and bright (stroma) pixels. A region of interest (highlighted in yellow) with a width of 1,500 μm centered on the foveal center was selected to compute the choroidal vascularity index (CVI). #Unpaired t-test for continuous data and Chi-square test for categorical data

Statistical Analysis

All assessments were performed in both the study and the fellow eyes. We analyzed all data using SPSS version 21.0 (SPSS, Chicago, IL). Descriptive data (age, sex, duration of symptom) are presented as means ± SDs. Baseline characteristics were used Unpaired *t*-test for continuous data and Chi-square test for categorical data. We analyzed pairwise comparisons of data (BCVA, CST, SFCT, CVI, the total choroidal area, and the luminal and stromal areas) between baseline and 1- and 3-month values using repeated ANOVA measures with Bonferroni correction. We applied unpaired *t*-tests to compare means between the study groups and between baseline and follow-up values within groups and paired *t*-test to compare between study eyes and fellow eyes. We considered *P* values < 0.05 as indicative of statistical significance.

Results

Our study included records of 34 patients: 16 patients (16 eyes) in the spironolactone (SPRL) group and 18 patients (18 eyes) in the PDT group. The baseline characteristics of the two groups were similar (Table 1); 3 patients in the PDT group had prior steroid use, whereas none of the patients in the spironolactone group had been prescribed steroids before. In addition, the groups were well balanced in terms of age (mean age ± SD, 50.13 ± 11.41 years in the spironolactone group, 49.17 ± 8.90 years in the PDT group; $P = 0.785$), proportions of women:men (2:14 and 1:17; $P = 0.591$), duration of symptoms (7.44 months and 7.67 months; $P = 0.868$), and baseline BCVAs (0.48 and 0.40 logMAR; $P = 0.391$).

Table 1 Demographic data

Demographic data	Spironolactone (N = 16)	PDT (N = 18)	*P*
Mean age ± SD (years)	50.13 ± 11.41	49.47 ± 8.75	0.785
Sex: male (%)	14 (87.5)	17 (94.4)	0.597
Underlying disease (%)			
Hypertension	3 (18.8)	8 (44.4)	0.152
Diabetes	2 (12.5)	2 (11.1)	1.000
Dyslipidemia	1 (6.3)	3 (16.7)	0.604
Smoking (%)	4 (25.0)	4 (22.2)	1.000
Insomnia (%)	4 (25.0)	1 (5.6)	0.164
Stress (%)	5 (31.3)	3 (16.7)	0.429
History of corticosteroid use (%)	0 (0.0)	3 (16.7)	0.230
Duration of symptom (months)	7.44 ± 4.50	7.67 ± 3.45	0.868

[#]Unpaired *t*-test for continuous data and Chi-square test for categorical data

Choroidal vascularity index (CVI), and total choroidal, luminal, and stromal areas

The baseline CVIs were 60.33% in the spironolactone group and 60.51% in the PDT group ($P = 0.894$). After treatment, the CVIs increased slightly (not statistically significant) to 61.72% and 61.28 % at 1 and 3 months, respectively, in the spironolactone group. However, in the PDT group, the CVIs increased significantly to 63.35% ($P = 0.004$) at the 1-month follow-up and o 63.56% ($P = 0.001$) at the 3-month follow-up (Table 2).

The total choroidal areas at baseline were 2.25 mm^2 in the spironolactone group and 2.18 mm^2 in the and PDT group, but only the PDT group showed a statistically significant decrease ($P = 0.016$ at month 1 follow-up, $P = 0.019$ at 3-month follow-up). This was primarily due to a reduction in stromal area in the PDT group from 0.87 mm^2 at baseline to 0.75 mm^2 at the 1-month follow-up ($P = 0.001$) and to 0.74 μm^2 at the 3-month follow-up ($P \leq 0.001$). The luminal areas did not change significantly in either group (Table 2).

Subfoveal choroidal thickness (SFCT)

The mean subfoveal choroidal thickness (SFCT) at baseline in the eyes with active CSC (study eyes; SE) tended to be thicker than those in the fellow eyes (FE), although the differences only reached statistical significance in the PDT group ($P = 0.031$). After treatment, the SFCTs in the study eyes decreased significantly from 397.13 μm to 359.88 μm at the 1-month follow-up ($P \leq 0.001$) and to 366.81 μm ($P = 0.013$) at the 3-month follow-up in the PDT group. However, in the spironolactone group, the SFCT reduction was not statistically significant, dropping from 430.94 μm at baseline to 417.94 μm at the 1-month follow-up ($P = 0.237$) and to 412.06 μm at the 3-month follow-up ($P = 0.195$; Table 2). The SFCTs in the fellow unaffected eyes remained similar in all groups (Table 2).

Central subfield thickness (CST)

In the spironolactone group, the mean CSTs decreased from 364.25 μm at baseline to 342.56 μm at the 1-month follow-up ($P = 1.000$) and to 273.31 μm at the 3-month follow-up ($P = 0.042$). In the PDT group, the mean CSTs decreased from 387.71 μm at baseline to 251.18 μm ($P = 0.002$) at the 1-month follow-up and remained at that level (254.00 μm) at the 3-month follow-up ($P \leq 0.001$; Table 2). By the 3-month follow-up, residual subretinal fluid was apparent in 50% of spironolactone eyes and in 33.33% of PDT eyes.

Best-corrected visual acuity (BCVA)

The mean visual acuities improved significantly at the 3-month follow-up in both groups, going from 0.48 LogMAR at baseline to 0.27 LogMAR in the spironolactone group ($P = 0.001$), and from 0.40 LogMAR to 0.23 LogMAR in the PDT group ($P = 0.006$; Table 2).

In the unaffected fellow eyes, the choroidal markers remained similar over time in both groups (Table 2).

Table 2 Impact of oral spironolactone or half-dose PDT in eyes with persistent CSC and in unaffected fellow eyes

	Spironolactone group				PDT group				$P^{\#}$
	Study eyes (n = 16)	$P^{\#}$	Fellow eyes (n = 12)	$P^{\#}$	Study eyes (n = 18)	$P^{\#}$	Fellow eyes (n = 17)	$P^{\#}$	
CVI (%)									
Baseline	60.33 ± 3.97		64.26 ± 2.79		60.51 ± 3.59		62.64 ± 4.39		0.894
1-month follow-up	61.72 ± 3.31	0.319	64.66 ± 4.31	1.000	63.35 ± 4.00	0.004	63.23 ± 3.65	1.000	0.227
3-month follow-up	61.28 ± 3.98	0.627	64.56 ± 3.37	1.000	63.56 ± 3.56	0.001	63.74 ± 3.74	0.545	0.102
Total choroidal area (mm^2)									
Baseline	2.25 ± 0.55		1.85 ± 0.33		2.18 ± 0.40		1.86 ± 0.55		0.711
1-month follow-up	2.19 ± 0.56	1.000	1.83 ± 0.39	1.000	2.01 ± 0.48	0.016	1.82 ± 0.55	0.934	0.342
3-month follow-up	2.20 ± 0.61	1.000	1.88 ± 0.41	1.000	2.00 ± 0.53	0.019	1.79 ± 0.51	0.282	0.336
Luminal area (mm^2)									
Baseline	1.34 ± 0.27		1.18 ± 0.18		1.31 ± 0.20		1.15 ± 0.30		0.747
1-month follow-up	1.34 ± 0.29	1.000	1.18 ± 0.20	1.000	1.26 ± 0.25	0.511	1.14 ± 0.29	1.000	0.427
3-month follow-up	1.33 ± 0.31	1.000	1.20 ± 0.22	1.000	1.26 ± 0.29	0.537	1.12 ± 0.27	0.912	0.503
Stromal area (mm^2)									
Baseline	0.91 ± 0.29		0.67 ± 0.16		0.87 ± 0.21		0.71 ± 0.27		0.696
1-month follow-up	0.85 ± 0.27	0.266	0.66 ± 0.21	1.000	0.75 ± 0.24	0.001	0.68 ± 0.27	1.000	0.281
3-month follow-up	0.87 ± 0.31	0.645	0.68 ± 0.20	1.000	0.74 ± 0.26	<0.001	0.66 ± 0.25	0.299	0.220
SFCT (μm)									
Baseline	430.94 ± 98.48		351.10 ± 68.60		397.13 ± 70.80		329.13 ± 103.45		0.274
1-month follow-up	417.94 ± 98.16	0.237	348.30 ± 66.88	1.000	359.88 ± 82.56	<0.001	318.67 ± 104.93	0.160	0.080
3-month follow-up	412.06 ± 102.57	0.195	336.30 ± 77.58	0.464	366.81 ± 93.35	0.013	313.80 ± 104.30	0.224	0.202
CST (μm)									
Baseline	364.25 ± 95.27				387.71 ± 177.52				0.643
1-month follow-up	342.56 ± 98.32	1.000			251.18 ± 56.04	0.002			0.002
3-month follow-up	273.31 ± 84.34	0.042			254.00 ± 64.29	<0.001			0.463
BCVA (LogMAR)									
Baseline	0.48 ± 0.26				0.40 ± 0.29				0.391
1-month follow-up	0.38 ± 0.22	0.274			0.30 ± 0.30	0.192			0.353
3-month follow-up	0.27 ± 0.16	0.001			0.23 ± 0.26	0.006			0.598

$P^{\#}$ significance level between baseline and follow-up values.

P^{*} significance level of difference between spironolactone and PDT groups.

Discussion

In this study on the treatment outcomes for eyes with CSC and persistent subretinal fluid, we observed significant differences between eyes treated with oral spironolactone and those treated with half-dose PDT. PDT was associated with a more rapid reduction in central subfield thickness (and resolution of subretinal fluid) and a more profound and rapid reduction in choroidal thickness. Interestingly, the stromal area (but not the luminal area) decreased over time after the treatment, particularly in the PDT group. This preferential reduction in the stromal component was reflected in the mean CVI, which showed an increase in the PDT group following treatment.

CVI is a relatively recent measure, although an extensive body of literature already mentions its potential application in the context of various diseases. For example, Agarwal and colleagues proposed CVI as a potentially useful marker to monitor panuveitis progression[35] and Vogt-Koyanaki-Harada disease (VKH).[36] Notably, baseline CVIs were higher in the panuveitis and VKH eyes compared to those in the normal controls, a finding that may indicate the presence of blood flow stasis in the choroid due to the inflammatory process. The CVIs decreased after the treatment. In studies on age-related macular degeneration (AMD) Xin Wei and colleagues[38] reported that the mean CVI in exudative AMD eyes was lower than that in the non-neovascular fellow eye due to a reduction in the luminal area. In another study of eyes with non-neovascular AMD without reticular pseudodrusen (RPD), the CVI was found to be lower in eyes with RPD than in normal control eyes.[39] These initial studies suggested that the CVI, along with the stromal and luminal areas, may be useful markers for monitoring changes in the vascular or stromal choroidal components.

Although the pathophysiology of CSC is unclear, the dilated vessels observed commonly in the outer choroid (Haller's layer) indicate that choroidal congestion may be pervasive. Given the prominence if these large vessels, one would presume that vessel engorgement and vascular volume increments should contribute to an increased CVI. Indeed, Agrawal and colleagues reported that the CVIs in CSC eyes were higher than in age-matched healthy eyes, and appeared to parallel the greater subfoveal choroidal thickness (SFCT) in the same eyes[34]. In recent study of shor term CVI change after PDT, Bazvand and colleagues found central macular thickness and CVI decreased after 6 weeks of PDT laser which explained that the mechanism of PDT in CSC disease is the recovery of choriocapillaris circulation[41]. In a similar manner, it would be reasonable to hypothesize that the thinning of the choroid that is observed with successful treatments (particularly after PDT), is driven by a reduction in the area of the engorged outer choroidal vessels. In our study, the luminal area decreased following PDT, but the reduction was not statistically significant. Instead, we found that the key driver of initial choroidal thinning following PDT was a statistically significant reduction in the stromal area at the 1-month follow-up. This greater reduction in the stromal area relative to that in the vascular area is reflected in the CVI increase following treatment. The pathophysiologic importance of the larger pre-treatment stromal area is emphasized by the fact that in both the spironolactone and PDT groups, the stromal area was larger in the study eyes than in unaffected fellow eyes. Given the presumed importance of the choroidal vasculature and hyperpermeability for the CSC pathophysiology, what is the function of the stroma in the pathophysiology? One hypothesis posits that the choroidal vascular changes can lead to an increase in hydrostatic pressure and a diffuse swelling of the choroidal stroma. Indeed, this may be the substrate for the large patches of hyperflourescence that are commonly seen on indocyanine green angiography images in these

patients. Sonoda and colleagues reported a larger hyperreflective area in the inner choroid, and they speculated that it was related to inflammation and edema of the choroidal stroma present in the setting of active CSC[42]. Chan and colleagues suggested that the main PDT action mechanism reduces this choroidal hyperpermeability[29].

Our study revealed a difference in the anatomic response to PDT and spironolactone. Whether the SFCT changes following spironolactone treatment is a controversial point[17,19-21,23]. For example, there were no SFCT changes after 3 months of spironolactone treatment in a study by Lee and colleagues[23] or after 1 year of treatment with spironolactone or eplerenone in another study by Ghadiali and colleagues[19]. By contrast, Zhao and colleagues observed a decrease 2 weeks after therapy initiation[17], Bousquest and colleagues showed a significant decrease after 1 month[20], and Durich and colleagues found a reduction in choroidal thickness in a recalcitrant CSC patient after 6 months of oral spironolactone or eplerenone[21]. In addition, skepticism over the potential therapeutic impact of mineralocorticoid antagonists has increased after a randomized trial of eplerenone failed to show efficacy for treating CSC. However, spironolactone is a more potent antagonist than eplerenone, and it should be ideally evaluated in a similar randomized trial. Regardless of the apparently contradictory evidence, in our study, we observed little impact of spironolactone on the total choroidal, luminal, and stromal areas or CVIs. The SFCT decreased slightly over the 3 months of follow-up, but the reduction was not statistically significant. Despite this, we did observe a significant reduction in the CST (and subretinal fluid) and an vision improvement by the 3-month follow-up in the patients treated with spironolactone– the reduction in CST, however, was slower than that in the patients treated with PDT, who showed a dramatic reduction by the 1-month follow-up. Taken together, our findings suggest that, any impact of mineralocorticoid antagonists operate via different mechanisms that do not significantly involve the choroid, unlike the mechanisms of PDT.

Our study is not without limitations and these must be considered when interpreting our findings: First, our study was retrospective in nature and we cannot rule out ascertainment bias or unknown imbalances between the study arms. However, we are fortunate because all the participants were imaged using the same protocol. Second, our follow-up lengths were relatively short at three months. As a result, we were not able to detect long-term differences in the treatment arms in terms of visual acuity, recurrent disease activity, or further choroidal changes. Third, our sample size was relatively small. Although we observed significant differences in CVI and stromal area in the PDT arms, we were likely underpowered to detect smaller differences due to treatment effect, particularly in the spironolactone arm. However, this was a pilot study to evaluate CVI changes following treatment, and our findings can guide the design of future, large, prospective longitudinal studies. Finally, although the CVI computation methodology we used, based on binarization, has been well-established in the literature, the lack of histological assessments for comparison introduces uncertainty regarding the accuracy of classifying pixels as representing stromal tissue.

In summary, in this pilot study of CVI analysis after spironolactone and PDT therapy for CSC, we found that the CVI increased after PDT, but not after spironolactone treatment. Moreover, the CVI change was primarily driven by a reduction in stromal area. If confirmed in larger, prospective studies, these findings may provide new insights into the pathophysiology of CSC and response to therapy.

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References

1. Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. Retina 2013;33:1659-72.
2. Gallego-Pinazo R, Dolzo-Marco R, Gómez-Ulla MS, Freund KB. Pachychoroid disease of macula. Retina. Med Hypo Discov Innov Ophthalmol 2014;3.
3. Phasukkijwatana N, Freund KB, Dolzo-Marco R, et al. Peripapillary pachychoroid syndrome. Retina 2017;0:1-16.
4. Cheung CMG, Lee WK, Koizumi H, Dansingani K, Lai TYY, Freund KB. Pachychoroid disease. Eye 2019;33:14-33.
5. Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. Surv Ophthal 2013;58:103-26.
6. Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 1996;121:26-34.
7. Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N, Jaisser F, Behar-Cohen F. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. Retin Eye Res 2015; 48:82-118.
8. Spaide RF, Hall L, Haas A, Campeas L, Yannuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Indocyanine green videoangiography of older patients with central serous chorioretinopathy. Retina 1996;16:203-13.
9. Hayashi K, Hasegawa Y, Tokoro T. Indocyanine green angiography of central serous chorioretinopathy. Int Ophthalmol 1986;9:37-41.
10. Guyer DR, Yanuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green angiography of central serous chorioretinopathy. Arch Ophthalmol 1994;112:1057-62.
11. Tittl MK, Spaide RF, Wong D, Pilotto E, Yannuzzi LA, Fisher YL, Freund B, Guyer DR, Slakter JS, Sorenson JA. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol 1999;128:63-68.
12. Haimovici R, Gragoudas ES, Duker JS, Sjaarda RN, Eliott D. Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. Ophthalmology 1997;104:1653-60.
13. Iida T, Spaide RF, Negrao SG, Carvalho CA, Yannuzzi LA. Central serous chorioretinopathy after epidural corticosteroid injection. Am J Ophthalmol 2001;132:423-5.
14. Hurvitz AP, Hodapp KL, Jadgchew J, Solomon DJ, Stolldorf HS, Provencher MT. Central serous chorioretinopathy resulting in altered vision and color perception after glenohumeral corticosteroid injection. Orthopedics 2009;32.
15. Ezra N, Taban M, Behroozan D. Central serous chorioretinopathy associated with topical corticosteroids in a patient with psoriasis. J Drugs Dermatol 2011;10:918-21.
16. McGraw AP, Bagley J, Chen WS, Galayda C, Nickerson H, Armani A, Caprio M, Carmeliet P, Jaffe IZ. Aldosterone increases early atherosclerosis and promotes plaque inflammation through a placental growth factor-dependent mechanism. J Am Heart Assoc 2013;2:e000018.
17. Zhao M, Célérier I, Bousquet E et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. J Clin Invest 2012;122:2672-9.
18. Herold TR, Prause K, Wolf A, Mayer WJ, Ulbig

MW. Spironolactone in treatment of central serous chorioretinopathy a case series. Graefes Arch Clin Exp Ophthalmol 2014;252:1985-91.

19. Ghadiali Q, Jung JJ, Yu S, Patel SN, Yannuzzi LA. Central serous chorioretinopathy treated with mineralocorticoid antagonists: a one-year pilot study. Retina 2016;36:611-8.
20. Bousquet E, Beydoun T, Rothschild PR, et al. Spironolactone for nonresolving central serous chorioretinopathy: a randomized controlled crossover study. Retina 2015;35:2505-15.
21. Daruich A, Matet A, Dirani A, Gallice M, Nicholson L, Sivaprasad S, Behar-Cohen F. Oral mineralocorticoid receptor antagonists: real-life experience in clinical subtypes of nonresolving central serous chorio-retinopathy with chronic epitheliopathy. Trans Vis Sci Tech 2016;5:2.
22. Herold TR, Rist K, Priglinger SG, Ulbig MW, Wolf A. Long-term results and recurrence rates after spironolactone treatment in non-resolving central serous chorio-retinopathy (CSCR). Graefes Arch Clin Exp Ophthalmol 2017;255:221-9.
23. Lee JH, Lee SC, Kim H, Lee CS. Comparison of short-term efficacy between oral spironolactone treatment and photodynamic therapy for the treatment of nonresolving central serous chorioretinopathy. Retina 2017;0:1-7.
24. Sun X, Shuai Yuanlu, Fang Wangyi. Jia Li, Weizhong Ge, Songtao Yuan, Qinghuai Liu. Spironolactone versus observation in the treatment of acute central serous chorioretinopathy. Br J Ophthalmol 2018;102:1060-5.
25. Lotery A, Sivaprasad S, O'Connell A, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previous untreated disease for more than 4 months(VICI): a randomized, double-blind, placebo-controlled trial. Lancet 2020;395:294-303.
26. Nicolò M, Zoli D, Musolino M, Traverso CE. Association between the efficacy of half-dose photodynamic therapy with indocyanine green angiography and optical coherence tomography findings in the treatment of central serous chorioretinopathy. Am J Ophthalmol 2012;153:474-480.e1.
27. Ober MD, Yannuzzi LA, Do DV, Spaide RF, Bressler NM, Jampol LM, Angelilli A, Eandi CM, Lyon AT. Photodynamic therapy for focal retinal pigment epithelial leaks secondary to central serous chorioretinopathy. Ophthalmology 2005;112:2088-94.
28. Sakalar YB, Keklikci U, Unlu K, Alakus MF, Kara IH. Effects of photodynamic therapy with verteporfin for the treatment of chronic central serous chorioretinpathy: an uncontrolled, open-label, observation study. Curr Ther Res Clin Exp 2010;71:173-85.
29. Chan WM, Lam DS, Lai TY, Tam BS, Liu DT, Chan CK. Choroidal vascular remodeling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at a primary disease level. Br J Ophthalmol 2003;87:1453-8.
30. Schimidt-Erfurth U, Laqua H, Schlötzer-Schrehard U, Viestenz A, Naumann GO. Histopathological changes following photodynamic therapy in human eyes. Arch Ophthalmol 2002;120:835-44.
31. Izumi T, Koizumi H, Maruko I, Takahashi Y, Sonoda S, Sakamoto T, Iida T. Structural analyses of choroidal after half-dose verteporfin photodynamic therapy for central serous chorioretinopathy. Br J Ophthalmol 2016;0:1-5.
32. Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. Ophthalmology 2010;117:1792-9.
33. Agrawal R, Gupta P, Tan K-A, Cheung CMG, Wong TY, Cheng C-Y. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. Sci Rep 2016;6:21090.
34. Agrawal R, Chhablani J, Tan K-A, Shah S, Sarviya C, Banker A. Choroidal vascularity index in central serous chorioretinopathy. Retina 2016;0:1-6.
35. Agrawal R, Salman M, Tan K-A, Karampelas M, Sim DA, Keane PA, Pavesio C. Choroidal vascularity index (CVI) – A novel optical coherence tomography parameter for monitoring patients with panuveitis? PLOS ONE 2016;11:e0146344. doi:10.1371/journal.pone.0146344.
36. Agrawal R, Li LKH, Nakhate V, Khandelwal N,

Mahendradas P. Choroidal vascularity index in Vogt-Koyanaki-Harada disease progression. Trans Vis Sci Tech 2016;5:7. doi:10.1167/tvst.5.4.7.

37. Koh LHL, Agrawal R, Khandelwal N, Sai Charan LS, Chhablani J. Choroidal vascular changes in age-related macular degeneration. Acta Ophthalmol 2017;95:e597-e601.
38. Wei X, Ting DSW, Ng YW, Khandelwal N, Agrawal R, Cheung CMG. Choroidal vascularity index A novel optical coherence tomography based parameter in patients with exudative age-related macular degeneration. Retina 2016;0:1-6.
39. Velaga SB, Nittala MG, Vupparaboina KK, Jana S, Chhablani J, Haines J, Pericak-Vance MA, Stambolian D, Sadda SR. Choroidal vascularity index and choroidal thickness in eyes with reticular pseudodrusen. Retina 2019;00:1-6.
40. Kinoshita T, Mitamura Y, Mori T, Akaiwa K, Semba K, Egawa M, Mori J, Sonoda S, Sakamoto T. Changes in choroidal structures in eyes with chronic central serous chorioretinopathy after half-dose photodynamic therapy. PLOS ONE 2016;11:e0163104. doi:10.1371/journal.pone.0163104.
41. Fatemeh Bazvand, Hassan Asadigandomani, Alireza Nezameslami, Reza Sadeghi, Mahdi Soleymanzadeh, Alireza Khodabande and Hamid Riazi-Esfahani. Short term choroidal microvascular changes following photodynamic therapy in chronic central serous chorioretinopathy. Photodiagnosis Photodyn Ther. 2023 Dec:44:103807. doi: 10.1016/j.pdpdt.2023.103807. Epub 2023 Sep 20.
42. Sonoda S, Sakamoto T, Kuroiwa N, Arimura N, Kawano H, Yoshihara N, Yamashita T, Uchino E, Kinoshita T, Mitamura Y. Structiral changes of inner and outer choroid in central serous chorioretinopathy determined by optical coherence tomography. PLOS ONE 2016;11:e0157190. doi:10.1371/journal.pone.0157190.

การศึกษาการเปลี่ยนแปลงของ choroidal vascularity index ในการรักษาโรคจุดภาพชัดแยกชั้นจากน้ำรั่วเรื้อรังด้วยสไปโรโนแลคโตนเปรียบเทียบกับการรักษาด้วย photodynamic therapy

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บทคัดย่อ:

วัตถุประสงค์ของงานวิจัย: โรคจุดภาพชัดรั่วน้ำ (Central Serous Chorioretinopathy: CSC) ปัจจุบันพบว่าเป็นโรคที่มีความผิดปกติของชั้นคอรอยด์ โดยจะพบชั้นคอรอยด์หนาตัวขึ้น (Increased choroidal thickness) และเส้นเลือดในชั้นคอรอยด์มีการขยายตัวขึ้น (Dilated choroidal vessels) การวัดชั้นคอรอยด์ด้วยวิธี CVI (Choroidal vascular index) เป็นวิธีการวัดที่จะประเมินเส้นเลือดในชั้นคอรอยด์กับชั้นเนื้อเยื่อคอรอยด์ (choroidal stroma) ทำให้เห็นได้ว่า มีความผิดปกติที่ส่วนใดเป็นหลักการรักษาโรคจุดภาพชัดรั่วน้ำด้วยวิธีเลเซอร์Photodynamic therapy (PDT) และ Spironolactone ที่มีคุณสมบัติเป็น Minearalocorticoid antagonist เป็นหนึ่งในวิธีที่นำมาใช้ในการรักษาโรคจุดภาพชัดรั่วน้ำ โดยวัตถุประสงค์ในการศึกษานี้เพื่อดูการเปลี่ยนแปลงของชั้นคอรอยด์ โดยจะประเมินการเปลี่ยนแปลงของเส้นเลือดคอรอยด์และชั้นเนื้อเยื่อคอรอยด์ก่อนและหลังการรักษาด้วย Half-dose PDT และ spironolactone

รูปแบบการวิจัย: การศึกษาย้อนหลัง

วิธีการศึกษา: choroidal vascularity index (CVI) เป็นการศึกษาชั้นคอรอยด์ โดยนำภาพตัดขวางจอตา (Optical coherence tomography) มาวิเคราะห์สัดส่วนของ vascular/luminal pixels เทียบกับ total number of pixels โดยนำมาคิดเป็นเปอร์เซ็นต์ โดยการศึกษานี้นำผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคจุดภาพชัดแยกชั้นจากน้ำรั่วเรื้อรังที่ได้รับการรักษาด้วยด้วยสไปโรโนแลคโตน จำนวน 16 รายและ photodynamic therapy จำนวน 18 ราย มาเปรียบเทียบการเปลี่ยนแปลงของ CVI หลังได้รับการรักษาที่ 1 และ 3 เดือนตามลำดับ

ผลการศึกษา: พบว่ากลุ่มที่ได้รับสไปโรโนแลคโตนไม่มีการเปลี่ยนแปลงของ CVI ,กลุ่มที่ได้รับ photodynamic therapy มีการเปลี่ยนแปลงของ CVI ที่ 1 และ 3 เดือนอย่างมีนัยสำคัญทางสถิติ (60.51% เทียบกับ 63.35% และ 63.56% P = 0.004, 0.001) และพบว่าความหนาของชั้นคอรอยด์หลังได้รับการรักษาที่ 3 เดือนลดลง 30.32 μm (P = 0.013) ในกลุ่มที่ได้รับ photodynamic therapy เทียบกับ 18.88 μm (P = 0.195) ในกลุ่มสไปโรโนแลคโตน

สรุป: จากการศึกษาการรักษาด้วยสไปโรโนแลคโตนไม่พบการเปลี่ยนแปลงของชั้นคอรอยด์ ในขณะที่การรักษาด้วย photodynamic therpy มีความหนาของชั้นคอรอยด์ลดลงและ CVI เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ ดังนั้นการรักษาด้วย photodynamic therapy ส่งผลต่อการเปลี่ยนแปลงทางกายวิภาคของชั้นคอรอยด์มากกว่าสไปโรโนแลคโตน ซึ่งอาจส่งผลให้ประสิทธิภาพของการรักษาด้วย photodynamic therapy มีประสิทธิผลมากกว่าสไปโรโนแลคโตน

คำสำคัญ: โรคจุดภาพชัดแยกชั้นจากน้ำรั่ว, สไปโรโนแลคโตน

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Dr. Sadda reports honoraria from Amgen, Bayer, Genentech/Roche, Novartis, Allergan, 4DMT, Heidelberg, Optos, Nidek, and Centervue.

Drs. Taweebanjongsin, Piriyakoontorn, Chanwimol, Pooliam and Agrawal have no conflicts of interest to report.

Synopsis

The choroidal vascular index, reflecting the choroidal vascular status, changed significantly after photodynamic therapy, but remained virtually unchanged following spironolactone therapy in eyes with central serous chorioretinopathy.

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