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Retina

Subthreshold Micropulse Laser Versus Oral Spironolactone in Chronic Central Serous Chorioretinopathy: A Quasi-Randomized Controlled Trial

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Purpose: To compare the efficacy and safety of subthreshold micropulse laser (SML) and spironolactone therapy for treating chronic central serous chorioretinopathy (CSC).

Methods: This was a quasi-randomized controlled trial. Eligible patients were quasi-randomized at a 1:1 ratio to receive SML or oral spironolactone and were assessed at 3 months after treatment.

Results: A total of 84 patients (90 eyes) were randomly assigned to receive SML ($n = 45$) or spironolactone ($n = 39$) initially. At last follow-up, 59.5% of patients in the SML group had complete resolution of subretinal fluid (SRF) compared to 43.6% in spironolactone group ($P = 0.362$). The mean visual acuity did not significantly improve between the two groups (0.38 $\pm$ 0.44 vs. 0.43 $\pm$ 0.43 logMAR). The central retinal thickness was decreased from 335.06 $\pm$ 120.25 µm to 222.15 $\pm$ 94.90 µm in the SML group and from 308.02 $\pm$ 90.69 µm to 257.27 $\pm$ 102.28 µm in the spironolactone group. After treatment, subfoveal choroidal thickness, total choroidal area, and stromal and luminal choroidal area were significantly lower in the spironolactone group as compared to the SML group. During the entire visit, the recurrence rate of SRF was 9.1% in the SML group compared to 35.3% in the spironolactone group. Slight adverse events occurred more frequently in the spironolactone group (0% vs. 16%).

Conclusions: Both SML and oral spironolactone were effective and safe treatments to ameliorate retinal anatomical structures for chronic CSC. A lower recurrence rate and fewer adverse effects were observed in the SML group, and better choroidal structure recovery was seen in the spironolactone group.

Translational Relevance: The investigation of SML and oral spironolactone may inform evidence-based clinical decisions for chronic CSC patients.

Introduction

Central serous chorioretinopathy (CSC) is a pachychoroid spectrum disease characterized by focal serous neurosensory retinal detachment and is most common in men who are >20 to 60 years old.[1] It is now the fourth most common retinopathy and leads to visual loss, metamorphopsia, relative central scotoma, and disturbed contrast vision.[2] The pathophysiology and mechanism of CSC are complicated and not totally understood. Previous studies suggest that choroidal vascular abnormalities and retinal pigment epithelium (RPE) dysfunction cause fluid leakage and accumulation between the neurosensory and pigmental epithelium.[3] Persistent subretinal fluid potentially leads to RPE atrophy and photoreceptor lesions, causing further irreversible visual loss, which requires early intervention to avoid.[4]

Several types of laser and drug treatment modalities have been applied to treat chronic CSC. Photodynamic therapy (PDT) and subthreshold micropulse laser (SML) are superior to traditional laser treatment because of their greater efficacy and safety.[5–8] Unfortunately, due to the high cost and worldwide shortage of verteporfin, it is impossible to administer PDT

therapy in China. According to the results of the Pan-American Collaborative Retina Study (PACORES) and the PLACE Trial, SML therapy may be an alternative effective treatment for chronic CSC.[5,9] In addition to lasers, the oral drug mineralocorticoid receptor antagonist (MRA) has also been adopted for treating chronic CSC, but its efficacy has not been consistent across trials.[10,11] A recent meta-analysis synthesized all related studies and suggested that, although there might be no significant visual benefit, MRA can accelerate the recovery of retinal anatomic structure and prevent worsening irreversible visual loss.[12–14]

To date, no prospective study has compared SML using a 577-nm laser with oral MRA therapy. This prospective, quasi-randomized controlled trial aimed to compare the efficacy and safety of yellow subthreshold micropulse 577-nm laser with that of oral mineralocorticoid receptor antagonists (spironolactone) in treating patients with chronic CSC.

Methods

Study Design

This prospective, open-label, single-center, quasi-randomized controlled trial was conducted at West China Hospital, Sichuan University, in China, from August 2020 to January 2022 and registered on ChiCTR (identifier: ChiCTR2100044356). The study adhered to the tenets of the Declaration of Helsinki and was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (identifier: 20201187), and informed consent was obtained from all participating subjects before treatment.

Study Patients

Patients who were diagnosed with chronic CSC were enrolled. The inclusion criteria were as follows: (1) patients who had a duration of CSC greater than 3 months, which is defined as chronic CSC in traditional classifications; (2) patients with subretinal fluid (SRF) and total area of RPE alteration >2 disc area with or without active leakage, which also is defined as complex CSC in multimodal imaging classification, according to fundus fluorescence angiography (FFA) and fundus autofluorescence (FAF)[15]; (3) patients older than 18 years; and (4) patients who had no contraindications for laser or oral spironolactone therapy. The exclusion criteria were as follows: (1) patients who had any other retinal disease, such as choroidal neovascularization (CNV), or other retinal vascular diseases or maculopathies; (2) patients with myopia (a refractive diopter greater than 6 diopters); (3) patients who were receiving systemic treatment with exogenous corticosteroids, intraocular surgery, anti–vascular endothelial growth factor (VEGF) therapy, or traditional laser therapy; (4) patients with serum potassium $\geq$ 5.5 mmol/L or who were taking oral potassium supplements, other potassium-sparing diuretics, or angiotensin inhibitors; (5) patients who were pregnant; and (6) patients who were unable to undergo the fundus examination.

All patients underwent comprehensive ophthalmic examination, including Snellen best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp microscopy, and indirect fundus ophthalmoscopy. In addition, FFA, FAF, and spectral-domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany) and OCT angiography (OCTA; Carl Zeiss Meditec, Oberkochen, Germany) were performed for each patient at baseline. Except for FFA, other examinations were performed at 1 week, 1 month, and 3 months after the start of treatment, with the final evaluation occurring at the 3-month visit.

Randomization and Masking

The trial included two treatment groups: SML group and oral spironolactone group. Eligible patients were assigned to two groups based on the month of their first presentation, with patients presenting in odd-numbered months receiving SML and those presenting in even-numbered months receiving oral spironolactone. The trial was open label to both the investigators and the subjects.

Interventions

For the 577-nm SML treatments, a 577-nm yellow laser system (EASYRET; Quantel Medical, Cedex, France) was used in micropulse mode with standardized SML treatment parameters for all patients: 200-µm spot size, 200-ms exposure time, and 5% duty cycle. The power titration started at 400 mW with a monospot micropulse model until a visible graying reaction on the retina occurred, at which point the threshold power usually ranged from 600 to 1000 mW. The treatment power of the SML was reduced to 50% of the threshold power and usually ranged from 300 to 500 mW. The laser spots were arranged in a dense pattern with no space between each spot. All of the SML treatments were performed by one surgeon (SG) to ensure consistency. After the first treatment, if there

was residual SRF, supplementary SML treatment was performed monthly until total resolution.

For the oral spironolactone treatment, patients in the spironolactone group started spironolactone 20 mg/tid after meals, during which their serum potassium level was measured at each evaluation visit. If the patient's serum potassium level was normal, persistent treatment (20 mg/tid) was carried out until complete resolution of the SRF. The dose was decreased to 20 mg/bid for 1 month and then decreased to 20 mg/day for 2 months. The dose of spironolactone was decreased or discontinued if hyperkalemia or elevated serum creatinine occurred. For patients who took oral spironolactone for more than 3 months but whose OCT showed persistent undissolved SRF, the treatment regimen was changed to SML for rescue therapy. If there was a self-initiated change of treatment regimen or failure to follow the treatment regimen, those data were excluded.

Outcomes

The primary outcome was complete resolution of SRF at the 3-month evaluation visit. According to the degree of height/area decrease, two observers (SG, GG) divided the treatment efficacy into the following groups: (1) total, complete resolution of SRF; (2) partial, SRF height/area decreased more than 50% compared to baseline; or (3) none, SRF height/area decreased less than 50% or worse compared to baseline.[7,16] The secondary outcomes included the resolution time of SRF (to reach total), the number of treatments required to be effective (to reach total resolution), the BCVA, the retinal structure (including SRF height, SRF longest diameter, SRF area, and central retinal thickness [CRT]), and the choroidal structure and perfusion of affected and contralateral eyes. Moreover, any adverse events (AEs), including ocular AEs (e.g., post-SML treatment CNV, RPE damage) and any other AEs related to oral spironolactone, were noted.

Image Acquisition and Analysis

SPECTRALIS SD-OCT (Heidelberg Engineering) was utilized in this study and operates on six radial scans centered on the fovea. SRF area and height and CRT and subfoveal choroidal thickness (SFCT) measurements were made from horizontal and vertical scans sectioned using features of software included with the instrument. The longest diameter of the SRF was measured from the longest section of the SRF. All of the OCT measurements were performed independently by two examiners (SG, GG). If the measurements differed by more than 10%, a third examiner (YZ) performed the measurements. OCTA was performed using the ZEISS CIRRUS HD-OCT 5000 with 6 × 6-mm OCT angiograms and CIRRUS AngioPlex automated segmentation of full-thickness retinal scans. Two examiners (SG, GG) performed the necessary manual segmentation to ensure accurate results if segmentation errors occurred. AngioPlex incorporates FastTrac retinal-tracking technology to reduce motion artifacts. All scans were independently completed by one examiner (YZ) for quality evaluation. All of the images were examined with ImageJ 1.52a (National Institutes of Health, Bethesda, MD) and binarized using the Phansalkar method with a radius of 15 pixels.[17] This process of binarization helped to convert the images into binary images, allowing further quantitative analysis and assessment of choroidal structures and perfusion. On the binarized OCT images, dark pixels were defined as the luminal choroid and white pixels were defined as the stromal choroid. In the binarized choriocapillaris and choroidal OCTA images, white pixels represented the vasculature and black pixels represented the flow deficits. The following metrics were quantified: total choroidal area, stromal choroidal area (SCA), luminal choroidal area (LCA), percentage of LCA (LCA/total choroidal area), choriocapillaris density, and choroidal density.

Statistical Analysis

All of the data were evaluated using SPSS Statistics 26.0 (IBM, Chicago, IL) for the statistical analysis. The variables were checked for normality with the Shapiro–Wilk test. Continuous data are presented as the mean ± standard deviation (SD) or median (interquartile range), and categorical variables are presented as counts and percentages. The differences between groups were evaluated by Student's t-test, Mann–Whitney U test, and Pearson's χ^2 test for continuous and categorical variables. Wilcoxon's rank-sum test was used to evaluate categorical variables between two groups. Repeated-measures continuous variable data were tested by a mixed linear model and adjusted for multiple comparisons within and between groups using the Bonferroni method. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 103 patients (109 eyes) with chronic CSC were screened in the present study. Nineteen partic-

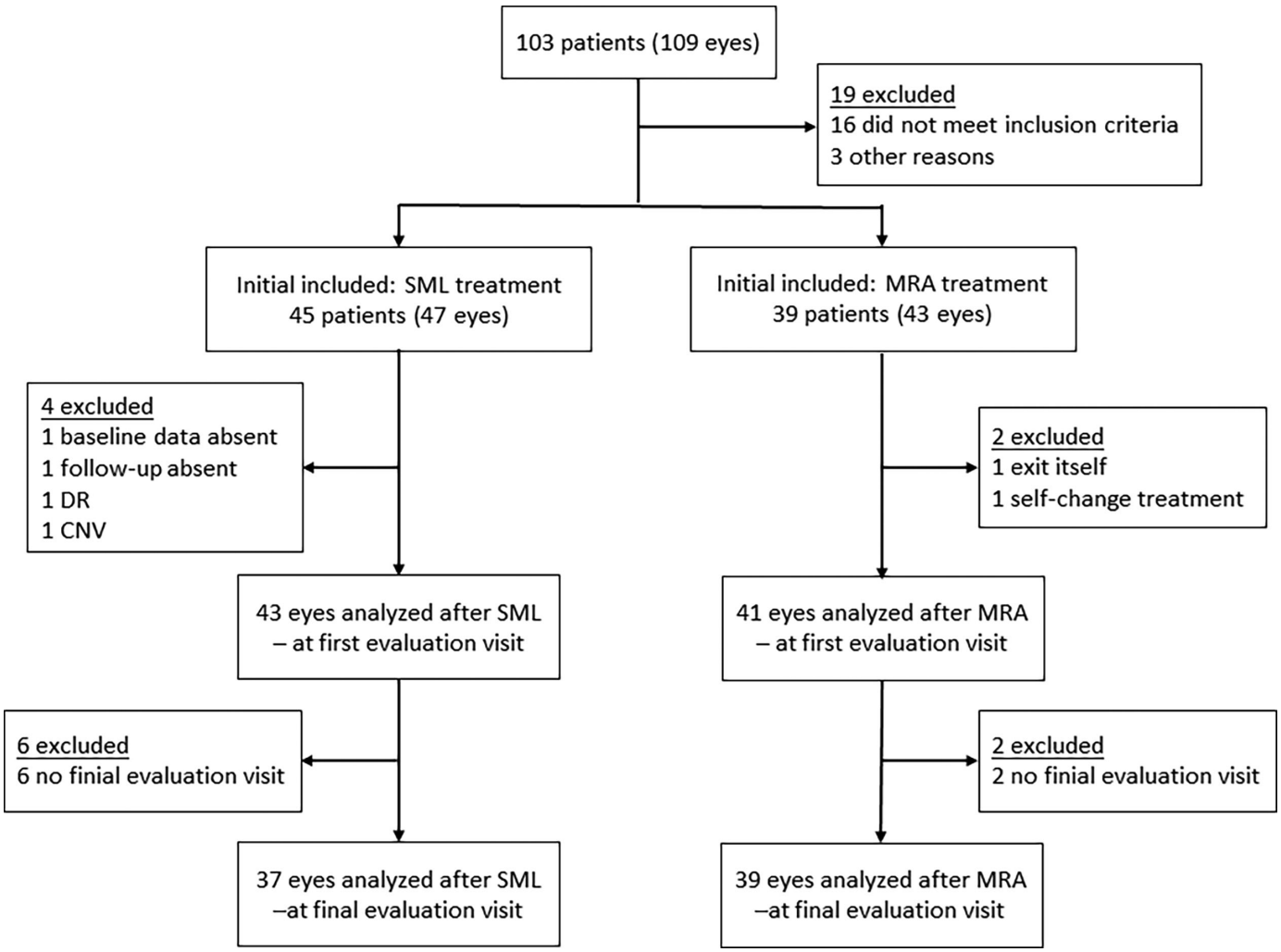

Figure. Study design flowchart. DR, diabetic retinopathy.

ipants were excluded due to disagreement or failure to meet the inclusion criteria. The other 84 patients (90 eyes) were quasi-randomized into the SML group or spironolactone group. The selection criteria for the patients are shown in the Figure. Finally, 37 eyes were enrolled for the SML group and 39 eyes for the spironolactone group. At the 3-month evaluation visit, eight patients (six in the SML group and two in the spironolactone group) had not adhered to the study protocol, and we did not obtain their final evaluation visit data.

The baseline characteristics of the patients in the study cohort are summarized in Table 1. The SML group included 35 men and six women, and the spironolactone group included 29 men and eight women. The mean ± SD ages of the patients in the SML group and spironolactone group were 46.95 ± 9.63 and 47.83 ± 9.04 years, respectively (P = 0.677). The mean duration of visual symptoms at the baseline visit was 17.28 ± 27.66 months in the SML group and 16.63 ± 23.24 months in the spironolactone group (P = 0.911). No significant differences were found between the two groups in terms of systemic state or baseline clinical characteristics, including the mean BCVA, SRF, CRT, and SFCT (all $P > 0.05$). Notably, the mean SFCT in both the affected and contralateral eyes of all of the patients met the criteria for pathological pachychoroid (SFCT > 300 µm).

At the 3-month evaluation visit, 22 of the 37 eyes in the SML group (59.5%) had total resolution of SRF, whereas 17 of the 39 eyes in the spironolactone group (43.6%) had total resolution (P = 0.362). The rates of total added partial resolution of SRF were 81.1% and 76.9% in the SML and spironolactone groups, respectively. The resolution times of SRF were 1.45 ± 1.01 months and 1.39 ± 1.24 months in the SML and spironolactone groups, respectively (P = 0.855). In

Table 1. Patient Demographics and Baseline Characteristics

	SML Treatment ($n = 41$)	Spironolactone Treatment ($n = 37$)	χ^2/t	P
Age (y), mean ± SD	46.95 ± 9.63	47.83 ± 9.04	0.42	0.677
Gender, *n* (%)			0.64	0.422
Female	6 (14.6)	8 (21.6)		
Male	35 (85.4)	29 (78.4)		
Duration (months), mean ± SD	17.28 ± 27.66	16.63 ± 23.24	0.11	0.911
Systemic state, *n* (%)				
Smoker	18 (43.9)	14 (37.84)	0.30	0.586
Systemic steroid	1 (2.44)	0 (0)	0.91	0.339
Hypertension	4 (9.76)	2 (5.41)	0.52	0.472
Diabetes	4 (9.76)	2 (5.41)	0.52	
BCVA (logMAR), mean ± SD	0.39 ± 0.41	0.42 ± 0.39	—	0.698
SRF, mean ± SD				
Height (µm)	168.17 ± 98.12	135.71 ± 71.74	—	0.069
Longest diameter (µm)	2900.58 ± 1479.32	2445.15 ± 1199.24	—	0.153
Area (mm^2)	0.29 ± 0.27	0.18 ± 0.14	—	0.008*
CRT (µm)	335.06 ± 120.25	308.02 ± 90.69	—	0.223
SFCT (µm)	445.37 ± 112.50	449.46 ± 113.67	—	0.865

*Significant differences were found between the SML group and the spironolactone group.

addition, the number of SML treatments required to be effective was 1.45 ± 0.51. At the 1-month evaluation visit, 27.9% and 29.3% of the eyes in the SML and spironolactone groups, respectively, had total resolution of SRF ($P = 0.890$). At the 3-month evaluation visit, SRF recurred in two eyes in the SML group (9.1%) and in six eyes in the spironolactone group (35.3%) ($P = 0.059$) (Table 2).

At the whole evaluation visit, the mean BCVA in both groups remained relatively stable, and there was no statistically significant difference between the two groups. After SML or spironolactone treatment, the height, longest diameter, and area of SRF decreased by varying degrees. However, the difference was not statistically significant between the SML group and spironolactone group at the whole evaluation visit. The spironolactone group exhibited a certain degree of rebound in the SRF area at the final evaluation visit. In addition, both groups showed significant improvements in the reduction in CRT, but the two groups did not significantly differ from each other (Table 2). OCT images for the chronic CSC patients in the SML and spironolactone groups are depicted in Supplementary Figure S1 and Supplementary Figure S2, respectively.

Changes in the permeability of choroidal vessels after oral spironolactone treatment were observed and summarized in Table 3. The choroidal structure exhibited significant changes at the final evaluation visit in the spironolactone group. The mean SFCT decreased statistically significantly, from 449.46 ± 113.67 µm at baseline to 409.27 ± 121.58 µm at the final evaluation visit in the spironolactone group. In addition, in the spironolactone group, the total choroidal area, SCA, and LCA were significantly lower at the final evaluation visit than in the SML group. Notably, these changes not only occurred in the affected eyes but also influenced the contralateral eyes. However, there was no significant decrease in choroidal vascular perfusion, including choriocapillaris density or choroidal density, nor was there a difference between the SML group and spironolactone group.

At the whole evaluation visit, the IOP was maintained at normal and stable in the SML and spironolactone groups. The serum potassium concentration in the spironolactone group was within the normal range, and there was no significant change after oral spironolactone treatment. The AEs related to treatment of all patients during the whole evaluation visit are shown in Table 4. No patients in the SML group reported any AEs. There was no post-SML treatment CNV or RPE damage in the SML group. Among the participants receiving oral spironolactone, six patients (16%) reported various AEs. The more common adverse events included gastrointestinal irritation and neurological and endocrine system disorders; most of these AEs were tolerated by the patients and did not require special treatment.

Table 2. Treatment Effect of Primary and Secondary Outcome Measures

Outcome Measure	SML Treatment ($n = 37$)	Spironolactone Treatment ($n = 39$)	χ^2/t	P
Resolution of SRF, *n* (%)			2.03	0.362
Total	22 (59.5)	17 (43.6)		
Partial	8 (21.6)	13 (33.3)		
None	7 (18.9)	9 (23.1)		
Resolution time of SRF (months), mean ± SD	1.45 ± 1.01	1.39 ± 1.24	0.18	0.855
Number of treatments required to be effective, mean ± SD	1.45 ± 0.51	—	—	—
Resolution of SRF at 1 month, *n* (%)			0.02	0.890
Yes	12 (27.9)	12 (29.3)		
No	31 (72.1)	29 (70.7)		
Recurrence of SRF within 6 months, *n* (%)	2 (9.1) ($n = 22$)	6 (35.3) ($n = 17$)	—	0.059
BCVA, mean ± SD				
At first evaluation visit	0.37 ± 0.40	0.37 ± 0.40	—	0.651
At final evaluation visit	0.38 ± 0.44	0.43 ± 0.43	—	0.430
SRF, mean ± SD				
Height (µm)				
At first evaluation visit	111.45 ± 82.69†	99.50 ± 73.85	—	0.348
At final evaluation visit	55.07 ± 72.52†	85.93 ± 90.55†	—	0.475
Longest diameter (µm)				
At first evaluation visit	2497.45 ± 1838.48	1802.91 ± 1287.82†	—	0.082
At final evaluation visit	1244.03 ± 1571.81†,‡	1679.57 ± 1539.48†	—	0.920
Area (mm^2)				
At first evaluation visit	0.21 ± 0.29	0.12 ± 0.12	—	0.036*
At final evaluation visit	0.08 ± 0.12†	0.13 ± 0.19	—	0.202
CRT				
At first evaluation visit	279.79 ± 110.69†	266.43 ± 89.82	—	0.357
At final evaluation visit	222.15 ± 94.90†	257.27 ± 102.28†,‡	—	0.135

*Significant differences were found between the SML group and the spironolactone group.
†Significant differences compared to the baseline data.
‡Significant differences were found compared to the first evaluation visit.

Discussion

CSC is a common and self-limited fundus lesion, but persistent SRF can cause irreversible damage to photoreceptor cells, multifocal or diffuse RPE disruption, and atrophy throughout the posterior pole. Early treatment and rapidly promoting SRF regression are keys to protecting the anatomical morphology and function of photoreceptor cell–RPE structures.[1,18] Although a variety of effective therapies have been proposed, comparisons of each therapy are still inconclusive, and the treatment regimen has not reached a consensus. Limited by the shortage of verteporfin, the most common treatment regimens in China include SML and oral MRA therapy. Our study designed a quasi-randomized controlled trial and aimed to compare the efficacy and safety of SML and oral spironolactone for chronic CSC patients, for which there is a shortage of evidence in published studies.

In our study, nearly half of the patients achieved complete SRF resolution at the 3-month evaluation visit, and the proportion of resolution in the SML group (59.5%) was slightly greater than that in the spironolactone group (43.6%). Such a finding was a primary aim of our trial because complete SRF

Table 3. Choroidal Structure and Perfusion of Affected Eyes and Contralateral Eyes

Outcome Measure	Affected Eyes, Mean ± SD			Contralateral Eyes, Mean ± SD		
	SML Treatment ($n = 43$)	Spironolactone Treatment ($n = 41$)	*P*	SML Treatment ($n = 43$)	Spironolactone Treatment ($n = 41$)	*P*
SFCT (μm)						
Baseline	445.37 ± 112.50	449.46 ± 113.67	0.865	402.21 ± 123.47	372.65 ± 127.40	0.329
At final evaluation visit	469.37 ± 104.02	409.27 ± 121.58†	0.159	417.96 ± 123.53	350.25 ± 134.38†	0.139
Total choroidal area (mm^2)						
Baseline	3.83 ± 1.37	3.57 ± 1.10	0.340	3.36 ± 1.32	3.01 ± 1.16	0.237
At final evaluation visit	4.17 ± 1.32	3.18 ± 1.12†	0.030*	3.57 ± 1.33	2.76 ± 1.11†	0.034*
SCA (mm^2)						
Baseline	1.18 ± 0.44	1.09 ± 0.36	0.320	1.18 ± 0.44	1.09 ± 0.36	0.193
At final evaluation visit	1.27 ± 0.42	0.99 ± 0.37†	0.062	1.27 ± 0.42	0.99 ± 0.37†	0.032*
LCA (mm^2)						
Baseline	2.65 ± 0.95	2.48 ± 0.75	0.357	2.33 ± 0.90	2.10 ± 0.80	0.262
At final evaluation visit	2.90 ± 0.92	2.19 ± 0.75†	0.023*	2.48 ± 0.91	1.92 ± 0.77†	0.036*
Percentage of LCA (%)						
Baseline	69.37 ± 2.13	69.60 ± 1.77	0.575	69.55 ± 1.90	69.84 ± 1.58	0.471
At final evaluation visit	69.62 ± 2.02	69.21 ± 1.92	0.315	69.62 ± 1.46	69.52 ± 1.64	0.969
Choriocapillaris density (%)						
Baseline	51.23 ± 7.45	52.96 ± 7.70	0.478	61.64 ± 7.88	62.27 ± 7.55	0.802
At final evaluation visit	53.40 ± 6.48	54.08 ± 9.23	0.934	60.25 ± 9.41	61.75 ± 7.36	0.740
Choroidal density (%)						
Baseline	42.36 ± 8.32	41.46 ± 7.83	0.703	37.93 ± 7.50	36.39 ± 5.98	0.498
At final evaluation visit	41.67 ± 4.60	40.07 ± 7.75	0.782	37.92 ± 6.47	37.71 ± 7.03	0.963

*Significant differences were found between the SML group and the spironolactone group.
†Significant differences compared to the baseline data.

Table 4. Adverse Events

	SML Treatment ($n = 41$)		Spironolactone Treatment ($n = 37$)	
Type	AEs, *n* (%)	SAEs, *n* (%)	AEs, *n* (%)	SAEs, *n* (%)
Ocular				
Eye pain	0 (0)	0 (0)	0 (0)	0 (0)
Eye swelling	0 (0)	0 (0)	0 (0)	0 (0)
Intraocular pressure increase	0 (0)	0 (0)	0 (0)	0 (0)
Vitreous floaters	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal				
Nausea	0 (0)	0 (0)	1 (2.7)	0 (0)
Decreased appetite	0 (0)	0 (0)	1 (2.7)	0 (0)
Abdominal pains	0 (0)	0 (0)	1 (2.7)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)
Acid reflux	0 (0)	0 (0)	1 (2.7)	0 (0)
Metabolic disturbance				
Hyperkalemia	0 (0)	0 (0)	0 (0)	0 (0)
Hypokalemia	0 (0)	0 (0)	0 (0)	0 (0)
Nervous				
Dizzy	0 (0)	0 (0)	2 (5.4)	0 (0)
Headache	0 (0)	0 (0)	1 (2.7)	0 (0)
Sleepless	0 (0)	0 (0)	1 (2.7)	0 (0)
Cardiovascular				
Palpitations	0 (0)	0 (0)	1 (2.7)	0 (0)
Tachycardia	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine				
Decreased libido	0 (0)	0 (0)	1 (2.7)	0 (0)
Erectile dysfunction	0 (0)	0 (0)	1 (2.7)	0 (0)
Male breast induration	0 (0)	0 (0)	1 (2.7)	0 (0)
Male breast tenderness	0 (0)	0 (0)	2 (5.4)	0 (0)

SAEs, serious adverse events.

regression is considered a prerequisite for preserving and/or restoring visual function. There was a significant decrease in SRF and CRT in both groups after treatment. Previous studies have confirmed the effectiveness of SML in the treatment of chronic CSC. Sun et al.[16] compared SML with conventional laser therapy through a double-blind RCT, and 63.63% of patients achieved complete regression of SRF after 3 months of SML treatment. Zhou et al.[19] reported 83.3% complete resolution of SRF after 3 months of SML therapy in a prospective study of 30 eyes with CSC. However, the effectiveness of MRA in the treatment of chronic CSC is still controversial. A portion of studies have reported that MRA is effective, with effective rates fluctuating between 38.9% and 67%.[3,20,21] A few studies have suggested that the efficacy of eplerenone is not superior to that of placebo for chronic CSC patients,[10,11] but the results are controversial, and the statistical designs had several shortcomings.[22,23] In addition, differences in the efficacy of spironolactone and eplerenone in the treatment of chronic CSCR have been observed, and spironolactone is generally considered more efficacious (although it has more side effects).[21] Currently, most studies and some meta-analyses assert that MRA is an effective treatment for improving the anatomic structure of the retina, which is consistent with our results.

At the whole evaluation visit, the recurrence rate of SRF in the spironolactone group (35.3%) was significantly greater than that in the SML group (9.1%). SML therapy acts on the RPE to restore pump function and barrier function.[24] A previous study suggested that SML could reduce the recurrence rate of acute CSC.[25] In contrast, spironolactone achieves its therapeutic effect by blocking mineralocorticoid receptors

without repairing damaged RPE cells.[26] On the other hand, relapse was more likely to occur during drug reduction or discontinuation, which suggests that a sufficient amount of spironolactone should be administered and that the patient should experience a slower dose reduction.

With respect to visual functional outcomes assessed at the 3-month evaluation visit, the BCVA of patients with chronic CSC did not significantly improve in either group because long-lasting SRF in chronic CSC could lead to irreversible damage to the RPE and neuroretina.[27] Vignesh et al.[28] reported comparable visual outcomes after SML or eplerenone treatment during a mean follow-up of 8 months, and baseline visual acuity was positively correlated with final visual acuity in both groups. Patients treated earlier recover better visual acuity and achieve restored retinal morphology. In contrast, several studies have reported limited satisfactory functional results in patients with long-lasting chronic diseases, and similar visual outcomes have been reported compared to our data.[11] Several clinical studies have reported prognostic factors for chronic CSC and indicate that the presence of an intact RPE layer and the integrity of the ellipsoid zone at baseline are associated with a tendency toward a satisfactory visual outcome.[29,30]

A favorable morphological outcome was also detected in our study. Our data indicated that oral spironolactone was not inferior to SML for treating chronic CSC with respect to retinal anatomical outcomes. Notably, spironolactone treatment had a more remarkable influence on choroidal morphological structures than SML therapy. Although the underlying pathogenesis of this disease has remained unclear, CSC is considered to be a pachychoroid spectrum disease.[21] Choroidal thickening and hyperpermeability, venous congestion, and leakage can result in RPE dysfunction, in which mineralocorticoid receptor overactivation plays an important role.[31] In our study, there were no significant changes in choroidal structure in patients treated with SML, consistent with previous studies in which the SML was primarily directed at the RPE layer rather than the choroidal layer.[24] In contrast, the SFCT, total choroidal area, SCA, and LCA of patients treated with spironolactone significantly decreased. This may be due to systemic MRA treatment blocking the abnormally activated mineralocorticoid receptor pathway, thereby reducing intravascular hydrostatic pressure and vascular permeability in the choroid and improving abnormally dilated choroidal vessels.[32] Although the LCA decreased but not the percentage of LCA, we speculated that the abnormal activation of mineralocorticoid receptors not only increased intravascular hydrostatic pressure but also caused intravascular fluid leakage to the extravascular interstitium, resulting in choroidal stromal edema.[33,34] Spironolactone treatment relieved choroidal stromal edema. Thus, the decreases in the LCA and total choroidal area were comparable after spironolactone treatment. Zhao et al.[31] reported that the vascular area and extravascular area of rat retinal tissue increased significantly after aldosterone treatment, which also confirmed this hypothesis.

Previous studies have suggested that the thickness of the choroidal capillary layer could decrease and that blood perfusion is relatively insufficient or even atrophied in hypertrophic choroidal spectrum diseases due to mechanical compression by dilation of choroidal blood vessels.[35,36] In our study, although the choroidal structure improved after spironolactone treatment, the blood flow density in the choroid and choriocapillaris did not significantly change for either the SML treatment or spironolactone treatment, suggesting that the two therapies did not influence blood perfusion in the choroid.

In our study, none of the 37 patients treated with spironolactone discontinued treatment due to AEs, similar to the results of the VICI trial.[11] However, various AEs, including gastrointestinal irritation and neurological and endocrine system disorders, still occur in patients treated with spironolactone.[37] Endocrine system AEs such as feminization of male breasts and erectile dysfunction might have some impact on the quality of life of young and middle-aged men, who have a high incidence of CSC.[38] In contrast to those in the spironolactone group, none of the patients who received SML in our study experienced an AE.

This study has several limitations. First, the sample size was relatively small, so larger sample sizes are necessary to further confirm the results. Second, the whole follow-up period was relatively short due to the poor patient compliance caused by COVID-19, so additional studies are needed to determine the efficacy and prognosis of SML or spironolactone in patients with chronic CSC. Third, due to a lack of verteporfin in China, we could not include PDT therapy. Also, a case-matched blank control arm (placebo treatment) was not included in our study due to the severity of chronic CSC in patients whose SRF persisted for a minimum duration of 4 months, and even a small amount of remaining SRF could lead to irreversible photoreceptor damage and persistent vision loss.

In summary, the results of our study indicated that SML and oral spironolactone were comparable for treating chronic CSC with respect to both efficacy and safety assessed at 3 months after the start of treatment. SML treatment had a relatively lower recurrence rate in the short term. Oral spironolactone could improve

the choroidal hypertrophy status of CSC patients to a certain extent, but a few adverse events must be considered. Importantly, SML and oral spironolactone are both inexpensive, accessible, and effective treatment options, as is verteporfin for PDT therapy, which is unavailable in many countries.

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