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Clinical Trial of Spironolactone Effect as a Treatment for Acute Central Serous Chorioretinopathy

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Abstract

Central serous chorioretinopathy (CSCR) is a vision-threatening eye disease with no validated treatment and unknown pathogens.The disease is seen in young and middle aged groups accompanied by recurrent or chronic progressive loss of visual acuity. Overreaction of mineralocorticoid receptor (MR) pathways has been implicated in pathophysiology of CSCR. No effective drug therapy has been seen for treatment of CSCR. The purpose of this study was to evaluate MR antagonists in treatment of Central serous chorioretinopathy, thus reducing the duration of illness and increasing the quality of life are considered critical. This study is adouble-blind randomized clinical trial (RCT) in patients admitted to Shahid Sadoughi hospital in 2014-2015. Totally 40 patients with a history of acute CSCR were randomized into two groups: Group A treated with placebo and group B treated with spironolactone25 mg/d. Patient demographic, visual acuity(BCVA, LogMAR) and CMT were measured at baseline, two and four weeks later (the Snellen chart and OCT). In improvement of central macular thickness (CMT) and best corrected visual acuity (BCVA), success of treatment was 72.2% (p value0.028). LogMAR change of 0.463 to 0.108 after one month (p value<0.001) showed positive effect of BCVA in the group treated with Spironolactone.In the treatment group, CMT changed from 550 μm to 311μm, with a 43.43% significant reduction. No drug related complication was observed. Early treatment in the acute phase of CSCR with spironolactone25 mg/d may have clinical efficacy in the improvement of BCVA and CMT changes.

Keywords: Central Serous Chorioretinopathy, Spironolactone, Mineralocorticoid Receptor.

Introduction

Central serous chorioretinopathy (CSCR) is a sight-threatening disease which is characterized by accumulation of serous subretinal fluid (SRF) leading to the localized area of detachment surrounding macula (Seong et al., 2009). The incidence of this disorder continues to increase. CSCR affects about 1 in 10000 people, with men affected more commonly than women (Liew et al., 2013). Male-to-female ratio is 8:1 to 10:1 (Haimovici et al., 2004). Spontaneous resolution of subretinal fluid occurs in 3 to 4 months with improvement of VA. Recurrences of CSSRare likely to occur in some patients (Regillo and Johnson, 2012). The usual presenting symptoms are significant loss of visual acuity and development of permanent visual loss (Ciardella, 2001).

Some retrospective studies suggested, type A personality, pregnancy, and Glucocorticoid as risk factors of CSCR (Albert et al., 2008). It is worth mentioning that patients with hypertension have a higher risk of developing CSCR (Eom et al., 2012). As far as medication is concerned, there was no effective medication (Regillo and Johnson, 2012; Ciardella, 2001). Multiple studies have shown that photodynamic therapy is a useful treatment for acute and chronic central serous chorioretinopathy (Ciardella, 2001). Focal laser photocoagulation may hasten resolution of fluid, however, final visual acuity and recurrence rates are unaffected. Therapeutically, there are limits which eventually minimize the possibility of resorting to certain treatments. To illustrate this, the photocoagulation lasercannot be performed in the foveal avascular zone (Regillo and Johnson, 2012); in a similar vein Laser therapy as an option in the treatment of CSCR can cause some adverse effects such as secondary choroidal neovascularization or central Scotoma interfering central vision (Ciardella, 2001).

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Systemic corticosteroids have been associated with occurrences, prolongation, exacerbation and recurrences of CSCR (Khairallah, Kahloun and Tugal-Tutkun, 2012). The connotation of corticosteroid use and the development of CSCR have led to the suggestion of anti-corticosteroids as a treatment (Abouammoh, 2015). Prior experiments in rodents by Zhao et al suggested that intravitreal injection of high dose glucocorticoids induces choroidal vessel dilation and leakage (Zhao et al., 2010).

Spironolactone acts functionally as a competitive inhibitor of the mineralocorticoid (aldosterone) receptor which possesses additional anti-androgen properties (Jaisser and Farman, 2016). Few case-series documented a reduction or complete resolution of SRF level (Bousquet et al., 2013). Spironolactone is commonly used for treating hyperaldosteronism, hypertension, and congestive heart failure. While effective, it may cause unwanted progestational and antiandrogenic side effects, manifested as gynecomastia, abnormal menstrual cycles, and impotence, which may limit its use (Herold et al., 2014).

In this report, we evaluated the effect of Spironolactone as a Mineralocorticoid antagonist in patients with acute CSCR.

Methods

This study is a double-blind randomized clinical trial (RCT) in patients were admitted to Shahid Sadoughi hospital in 2014-2015. The study was conducted in accordance with the principles of ethics, protection of human subjects in medical research. For each patient, the study protocol and procedure were fully explained, and consent was obtained, according to the Ethics Committee of Shahid Sadoughi university of medical sciences. On the whole 40 patients ranging in age from 23 to 40 years old with a history of acute CSCR were randomized into two groups:

The Placebo, lactose, was used in group A; the group B however,was treated with spironolactone25 mg/d. Both groups were treated for 4wk. It needs to be pointed out that none of the patients selected for the study had other ocular histories, or history of taking corticostroid medication. Furthermore, none of the patients were pregnant.

Demographic (age, gender, etc.) and visual acuity (BCVA, LogMAR) and mean central subfield thickness (CMT) were measured at baseline, then followed in two weeks and one month (4wk) later, the Snellen chart and optical coherence tomography (OCT) were used.

The sample size was set at 40 based on, 80% confidence Level. The standard deviation of visual acuity with correction (S = 0/1) and to achieve significant differences in mean visual acuity of at least 0.1. In this study, the percentage of missing cases were considered 15%.

Recruitment Criteria

For all patients, diagnosis based on the best corrected visual acuity (BCVA, converted to LogMAR visual acuity for analysis), routine eye examination, and imaging results by optical coherence tomography (OCT). Acute CSCR was defined as patients exhibited presence of subretinal fluid less than 4wk in our findings of CSCR.

Exclusion Criteria

Exclusion criteria: 1) History of multiple and recurrent CSR. 2) Current state of pregnancy. 3) Previous diagnosis of eye diseases, such as keratopathy, diabetic retinopathy, cataract. 4) History of corticosteroid use. 5) Previous diagnosis of severe primary disease, such as cardiovascular disease, renal disease, and hypertension. 6) Patients who cannot use spironolactone because of systemic disease.

Observation

Upon arrival to the clinic, patients' visual acuity (BCVA, LogMAR) and CMT were measured to obtain baseline information,then the patients were followed in two weeks.If the primary outcome measure was the20% reduction in CMT, treatment would continue until 4 weeks. The criteria for termination of observations were the symptoms worsening during treatment, resulting in the patient requiring immediate laser treatment, and the patient showing any drug related complication.

Results

The study is a double-blind randomized clinical trial (RCT) in which 40 patients were admitted in 2014-2015 were diagnosed with acute CSCR, 77% male, were randomly classified in control group A and intervention group B, treated with placebo and spironolactone25 mg/d respectively. Four patients were excluded because they didn't return and one patient was excluded because of choroid tuberculosis.

Baseline Characteristics

The average patient age was 35.82, ranging from 23 to 40 and the average baseline BCVA (LogMAR) was 0.43 (ranging from 0.1 to 1). There was no significant difference in the age, the sex, right or left eye, between two groups. The details are presented in Table 1.

Table 1. Characteristics of included patients in the study

Variables	Group A (PELACEBO)	Group B (SPIRONOLACTONE)	P
Age (range, a)	35.95 (23-40)	36.35 (25-40)	750
Sex (M/F)	16/4	15/5	0.705
Lateral (right/left)	14/4	12/8	0.239

Best Corrected Visual Acuity

Follow-up time was divided into baseline visit (before treatment), 2wk, and 4wk (one month).
In group A (placebo), the average baseline visual acuity was 0.496 LogMAR (range: 0.1-1 Logmar) and the average visual acuity was 0.465 LogMAR (range 0.1-1 LogMAR) at study completion. There was no significant decrease at the second follow- up period (4wk after treatment) compared with baseline (P=0.02). In group B (spironolactone), the average baseline visual acuity was 0.463 LogMAR (range: 0.1-1 LogMAR) and the average visual acuity was 0.108 LogMAR (range 0.00-0.7 LogMAR) at study completion. The decrease was statistically significant in the second follow-up period (4wk after treatment) compared with baseline (P= 0.02). During the follow-up, the visual acuity of 19 eyes improved (group A: 6 eyes; group B: 13 eyes); the differences in improved BCVA between the two groups before and after treatment were statistically significant (P<0.05, Figure 1).

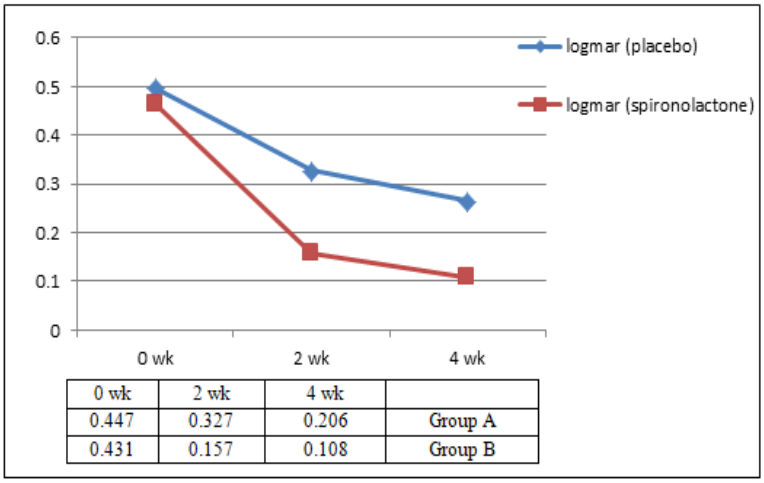

Fig. 1. Time course of the mean best corrected visual acuity of eyes with acute central serious chorioretinopathy that underwent drugs treatment in both groups.

Optical Coherence Tomography Analysis:

In group A (placebo), the average baseline CMT was 514 µm (range: 320.21 to 374.39 µm) and at study completion, the average CMT was 453 µm (range: 109.54-221.82 µm). There was no significant improvement of CMT in the placebo group.

In group B (spironolactone), the average baseline CMT was 550 µm (range: 312.32 to 378.53 µm) and at study completion, the average CMT was 311 µm (range: 109.54-221.82 µm). The decrease was statistically significant in the second follow-up period (4wk after treatment) compared with baseline (P<0.05, respectively). In comparison with group A (placebo) CMT in the group B (spironolactone) enjoyed a relatively more tangible improvement (P<0.05, Figure 2).

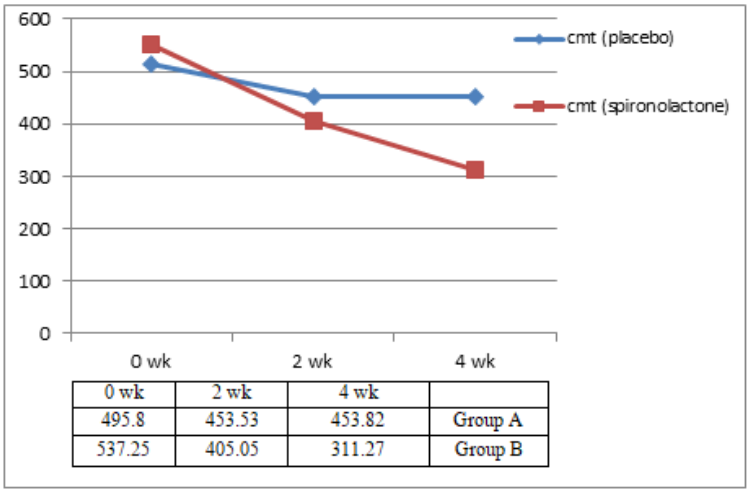

Fig. 2. Average CMT in both groups

After 4wk treatment, the cure rate of group A(placebo) was 35.3%, while the cure rate of group B(spironolactone) was 72.2%, as substantiated thought out the study, there was a statistical difference in total effective rate between two groups (P=0.028), as shown in Table 2.

Table 2. The cure rate of each group

	Success		Total
	Positive	Negative	
Group A (placebo)			
N	6	11	17
Percentage	35.3%	64.7%	100%
Group B (spironolactone)			
N	13	5	18
Percentage	72.2%	27.8%	100%
Total			
N	19	16	35
Percentage	54.3%	45.7%	100%

Discussion

40 patients diagnosed with acute CSCR, 77% male, were randomly classified in control group A and intervention group B, treated with placebo and spironolactone 25 mg/d respectively. In the group treated with Spironolactone, the positive effect of visual acuity was seen relatively higher. Overall success in improving visual acuity in the group treated with Spironolactone and CMT was 72.2% (p value=0.028).

The results of this study suggested that oral Spironolactone may be effective in the treatment of CSCR, and should be investigated as a potential treatment choice in acute cases.

Oral Spironolactone may be more beneficial than previous CSCR treatment modalities such as focal laser Photocoagulation or PDT, as it is a treatment that targets the entire retina versus specific areas (Bousquet et al., 2013). Additionally, laser photocoagulation treatment was not shown to reduce the incidence of recurrent or chronic CSCR and is more effective in acute CSCR (Gemenetzi, De Salvo and Lotery, 2010). Oral Spironolactone is also less invasive than laser treatment and anti-VEGF injections.

One difference in the results of the present study in comparison to the initial study by Eric K Chin (Chin et al., 2015) was the positive effect of treatment in visual acuity. In the present study, totally 35 patients with primary diagnosis CSCR were divided into two groups; the placebo and the group treated with oral Spironolactone (25 mg/d). The positive effect of visual acuity in the group treated with Spironolactone was observed with LogMAR change 0.463 to 0.108 after one month of treatment (p value <0.001), while Chin's study didn't exhibit any positive results whatsoever in this case (mean LogMAR 0.2 into 0.3).

In another study, Eric K Chin has evaluated the effect of antagonists Mineralocorticoid on CSCR. In this study 23 patients, included 7 newly diagnosed and 16 patients with exacerbation (relapse), were treated with Mineralocorticoid antagonists include Eplerenone and Spironolactone (therapeutic doses 25 to 50 mg twice a day) (Chin et al., 2015). Patients received oral therapy in a period of 2.3 ± 3.9 months.Chin's study showed a positive effect of treatment on the acute phase CSCR and decrease in CMT and MV (52.2%). In comparison with the relapse group, CMT in the newly diagnosed group was prone to more decrease.An improvement in vision was seen only in the newly diagnosed group (in the acute phase).

Similar to Chin's study, in our study CMT before treatment (550 μm) became 311 μm (with significant reduction of 239 μm after one month) (p value< 0.001). However, there was a little difference between both studies. In our study baseline mean of CMT was higher and all our patients were in the acute phase of CSCR. As mentioned in the Chin's study, treatment in the acute phase and newly diagnosed patients with Spironolactone had better results and our study confirmed this view. Consequently, compared to Chin's study, the present one seems to have proven more fruitful in terms of favorable outcomes, and this can be due to due to the lower dose and shorter duration of treatment.

In 2016 a clinical research was done by Yong Chai (2016) to evaluate the effect of Fenofibrate and Spironolactone on acute CSCR. Totally 60 patients (60 eyes) with a history of acute CSCR were randomized into two groups: group A with a combination therapy of Fenofibrate (200 mg) and Spironolactone (100 mg), and group B with only Fenofibrate (200 mg) once per day for 8wk. The changes of the visual acuity and other symptoms were observed. Finally, it showed Fenofibrate combined with Spironolactone may have more clinical efficacy in the treatment of CSCR than Fenofibrate only (Chai et al., 2016). In detail, CMT in group A decreased significantly to 49.5% and 37.0% in group B. In comparison with group A, CMT in our study decreased more, though we used the lower dose and shorter duration of treatment.

In Chai's study (2016) the best corrected visual acuity (BCVA, LogMAR) was improved to 0.22 and 0.27 after treatment from baseline of 0.35 and 0.36 in groups A and B (P<0.05). There were significant positive results in both studies. In our study, the positive effect of visual acuity in the group treated with Spironolactone was seen with Logmar change 0.463 to 0.157 after two weeks of treatment (p value< 0.001), whereas in Chai's study LogMARchange was 0.35 to 0.33 after two weeks of treatment, so as the chart shows there was a significant difference between speed of response to treatment in two groups. In neither of these two studies, side effects were reported.

In 2016 a prospective study published by Pichi F (2016),used the same dosing as Erick K Chin (2015) to evaluate the effect of oral spironolactone and eplerenone in CSCR.

In this study, sixty patients with persistent CSCR were assigned to three treatment groups. Twenty patients in Group 1 were treated with 25 mg of Spironolactone for 1 week, then the dose increased to 50 mg for the following 3 weeks, later the treatment shifted to Eplerenone 50 mg for 1 month. Twenty patients in Group 2 were treated with 25 mg of Eplerenone for 1 week, then the dose increased to 50 mg for 3 weeks, and later it shifted to Spironolactone 50 mg for 1 month. Twenty patients in Group 3 were treated with placebo for 1month, and later Spironolactone 50 mg was used as the treatment for 1 month (Pichi et al., 2016). In terms of BCVA, treatment in Group 1 was effective from the first month (Spironolactone, p value 0.01), and in Group 2, the treatment was effective from the second month (shift to Spironolactone, p value 0.004). Spironolactone is statistically superior to Eplerenone in improving BCVA of patients with CSCR, while both drugs can be considered equally effective in promoting the resorption of SRF (Pichi et al., 2016). In our study,BCVA in the group treated with Spironolactone started to range from 0.4 to 3.88 after one month (p value 0.004).

One difference in the present study in comparison to the initial study conducted by Kapoor KG, and Wagner AL (2016) was the variability in Spironolactone dosing. Within Kapoor's study, MR antagonists in the treatment of CSCRwere evaluated.

In the study mentioned above, 32 patients (12 Eplerenone 50 mg twice a day, 12 Spironolactone 50 mg twice a day, 8 observations) were enrolled in the study (Kapoor KG, Wagner, 2016). There was no difference between the positive effect of Eplerenone and Spironolacton, 75% of side effects were related to Spironolactone,thoughin our study, no side effect was reported and equally important, the lower dose of Spironolactone and the shorter duration of treatment could be considered another merit contributing to the success in our study.

This data supported the use of MR antagonists in CSCR and suggested an accelerated improvement compared to observation as same as our study.

Our results are comparable to a case report published by Zhao, M (2010). They treated 2 patients with chronic unresolved CSCR with oral eplerenone, for 5 weeks, and observed impressive and rapid resolution of retinal detachment and choroidal vasodilation as well as improved visual acuity (Jaisser and Farman, 2016). In this study patient 1, with CSCR more than 4 months with LogMAR0.2 (6/10), was treated with eplerenone (25 mg/d- increased 50 mg/d) resulted in almost total resorption of Subretinal fluid, with recovery of visual acuity in 0 (10/10). The treatment was stopped after 1 month, and no recurrence had occurred in 5 months later (Zhao et al.,

2010).Patient 2 had chronic and recurrent CSCR affecting the macula of the left eye for more than 6 years with a visual acuity of 1/10. He complained that his right eye vision dropped to 7/10. The patient received 25-50 mg/d eplerenone for 1 month. After 15 days of eplerenone 50 mg/d, both eyes showed total reduction of the subretinal fluid. Vision returned to 10/10 in the right eye and to 4/10 in the left eye. Their results identified MR signaling as a pathway controlling the choroidal vascular bed relaxation and provide a pathogenic link with human CSCR, which suggested that blockade of MR could be used therapeutically to reverse choroid vasculopathy (Zhao et al., 2010).

In our study, the positive effect of visual acuity in the group treated with spironolactone was seen with Logmar change from 0.4 to 0.1after one month (p value<0.001). The success of treatment was 72.2% to improve CMT and visual acuity.

We reported that Spironolactone acts as an effective medicine in patients with acute CSCR. The goal of Mineralocorticoid treatment for CSCR was to reduce and resolve SRF while improving visual outcomes.

It is important to see the effect of spironolctone in chronic and acute phase of CSCR. So, in 2013 Elodie Bousquet published a pilot study to evaluate the effect of MR-antagonism in the treatment of chronic CSCR. This study included 13 patients with CSCR of at least 4-month duration, treated with 25 mg/day of oral eplerenone for a week followed by 50 mg/day for 1 or 3 months. Eplerenone treatment was associated with a significant reduction in CMT (352 to 246 μm), subretinal fluid level, and an improvement in visual acuity (LogMAR 0.5 to 0.2 after 3 months) (Behar-Cohen Francine, 2014). Because the number of patients in this study was low, to complete, a prospective randomized controlled study was done by FrancineBehar-Cohen (2014) to test whether spironolcatone exerts the significant effect in chronic CSR.

Sixteen patients with chronic CSR (> 4 months) were randomized to either oral spironolactone (50mg/d) or placebo for 30 days then followed up to 90 days. The subretinal fluid and CMT were significantly reduced (67%) in the group treated with spironolactone but there was no change in BCVA. These results,like the ones we obtained in the present study, clearly showed a significant effect of Spironolactone after 30 days of treatment on CMT validating the hypothesis that MR is involved in CSR pathogenesis. Despite prior report (Behar-Cohen Francine, 2014) our patients' treatment showed the success of improvement in visual acuity.

In comparison with our study, visual acuity in Herold's improved less (Herold et al., 2014). In 2014,T.R.Herold evaluated treatment of 18 patients with chronic CSCR with Spironolactone 25 *mg*, twice a day.CMT at baseline (405 μm) reduced (287 μm)and Logmar 0.32 improved to Logmar 0.2 (Herold et al., 2014). In our study CMT of patients was much higher and visual acuity was in the worst situation. This difference may show the best effect of Spironolactone in acute CSCR more than chronic phase of CSCR disease.

Conclusion:

The purpose of this study was to examine the effectiveness of Spironolactone, as a treatment option for acute CSCR. The goal of Spironolactone treatment for acute CSCR was to reduce CMT while improving visual outcomes. Following therapy, there was a significant reduction in CMTand improved visual acuity in eyes with acute CSCR. The results of this study indicate that Spironolactone could be beneficial in the treatment of acute CSCR. No adverse events were found to be associated with the treatment.

Our study also has limitations, including the small number of patients; only the type with acute CSCR and the shorter follow-up period. Further studies will be needed to be able to individualize the recurrence or long-term effects of this multi-factorial illness.

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