Original Article

Using oral Rifampin to treat acute central serous Chorioretinopathy: a randomized placebo-controlled clinical trial

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ABSTRACT

This study investigated the possible therapeutic effects of oral rifampin on patients with acute Central Serous Chorioretinopathy (CSC). This clinical trial was a randomized placebo-controlled, double-masked research involving 30 patients with acute CSC. The patients were randomly assigned into two groups, one receiving 600 mg of oral rifampin once a day for a month and another being the matched placebo group. The Best Corrected Visual Acuity (BCVA), the subretinal fluid height at the posterior pole of the eye determined using spectral-domain optical coherence tomography (SD- OCT), and serum cortisol levels were assessed at baseline and an additional three months. The main outcome measures were the BCVA and subretinal fluid height and the secondary outcome measure was the serum cortisol level that was compared between groups.

At all follow-up times, significant improvements in BCVA and subretinal fluid resolution were found in both groups, but the differences between them were not statistically significant ($P > 0.05$). At baseline, the groups did not statistically differ in terms of mean 8 A.M. serum cortisol (C_{8AM}) ($P = 0.81$). Month 1, however, registered a significant difference in mean C_{8AM} between the groups ($P = 0.03$). At the end of the second month, this difference reverted to statistical nonsignificance ($P = 0.06$). The results suggested that the month-long treatment with oral rifampin exerted no beneficial effects on VA and subretinal fluid resolution in acute CSC patients. Such treatment, however, reduced the endogenous steroids of the oral rifampin group.

Keywords: Central serous chorioretinopathy, Rifampin, Subretinal fluid, Clinical trial

Introduction

Central Serous Chorioretinopathy (CSC), an idiopathic disorder of the posterior pole of the eye, is characterized by hyperpermeability and the dilation of choroidal vessels, leading to Serous neurosensory Retinal Detachment (SRD) and retinal Pigment Epithelial Detachment (PED) or dysfunction [1]. The characteristic fundoscopic view of CSC reflects well-localized SRD at the macula, with fluid accumulation under the sensory retina; diagnosis is confirmed via focal leaks from the Retinal Pigment Epithelium (RPE) on Fluorescein Angiography (FA) [2]. The disease can occur in acute or chronic form. Acute CSC typically develops in healthy individuals between the ages of 20 and 50 years, whereas chronic CSC manifests persistent subretinal fluid for at least 3 to 6 months [3]. The acute form of the disease causes intense localized serous detachment of the retina, with visual disturbance in the affected eye [4]. This is

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followed by a spontaneous resolution in the majority of patients, but the severe visual loss has been reported in 5% of cases [4].

Acute CSC is traditionally managed by observation alone, but the use of recent advances in technology, including adaptive optics, multifocal electroretinography, and microperimetry, have revealed significant anatomic and functional loss, even in eyes with a single episode of spontaneously resolved CSC with good Visual Acuity (VA) [5-9]. Because most CSC patients are of working age, visual symptoms may considerably interfere with their daily activities. Early intervention should therefore be considered. Currently, no standard therapy for acute CSC is available, even though many treatment modalities, such as thermal laser photocoagulation, photodynamic therapy with verteporfin, micropulse diode laser photocoagulation, and pharmacological agents, have been used as treatment [10-15]. These interventions are not appropriate for all cases, a problem that warrants research on novel solutions.

Given that corticosteroids are involved in CSC formation, glucocorticoid inhibition has been recommended as a possible therapeutic method [16-22]. Small-scale case series support the role of systemic anti-corticosteroid agents, including mifepristone, ketoconazole, finasteride, and rifampin, in the treatment of CSC [6, 23-27]. A few studies recently examined the impacts of mineralocorticoid receptor antagonists on CSC and endorsed the use of these agents in treating the disease [28-30], but these medications have not been included in the treatment protocols for CSC. Confirming the efficacy of orally administered drugs can clear the way for improving patient symptoms and preventing complications. In this regard, the role of rifampin in CSC treatment was introduced when the resolution of CSC occurred in a patient with tuberculosis and the induction of cytochrome P450 was suggested as a basic mechanism involved in the alleviation of CSC symptoms [16]. The presence of mineralocorticoid receptors in choroidal tissue and the change in the permeability of RPE, Bruch's membrane, and choriocapillaris by the corticosteroids are considered the most probable reason for this association [31].

With consideration of the above-mentioned issues, this study conducted a randomized controlled trial involving patients with acute CSC to evaluate the possible therapeutic effects of oral rifampin as an anti-corticosteroid agent on the resolution of subretinal fluid and the improvement of VA.

Materials and Methods

Study design

This research was of a randomized placebo-controlled, double-masked design. A sample of 30 patients with acute CSC was chosen from patients who were referred to the Emergency Department and Retina Clinic of Amiralmomenin Hospital, Rasht, Iran. Sampling was conducted between October 2015 and February 2018. All the patients were informed about other therapeutic modalities, the off-label situation of the therapy used in this work, and the possible side effects of rifampin. They all offered informed agreement, and the institutional Review Board and Health Research Ethics Committee of the Guilan University of Medical Science approved the research protocol. The trial was registered at http://www.irct.ir (identifier: IRCT2012072810414N1, registration location: Rasht, Iran).

Eligibility for participation was determined based on the following criteria: (1) acute CSC with a symptom duration lasting less than a month (2) and ages falling within the range of 20 to 60 years. A subject was evaluated as having acute CSC and included in the study if s/he exhibited SRD and PED or dysfunction without evidence of any other probable cause of the exudation, such as inflammation, infiltration, or choroidal neovascularization. The exclusion criteria were as follows:

1. Acute or chronic liver disease or abnormal baseline liver enzymes
2. Previous CSC attack(s)
3. Cushing's syndrome
4. Active tuberculosis
5. Pregnancy or lactation
6. Known sensitivity to rifampin
7. Drug consumption under a cytochrome-dependent metabolism
8. History of steroid intake during the past six months
9. Any other associated ocular disease
10. History of diseases with potential for retinal exudation, such as collagen vascular diseases and systemic hypertension
11. Organ transplantation
12. Alcoholism
13. Recent use of amphetamine-type stimulants
14. History of phosphodiesterase-5 inhibitor intake during the past six months

The included patients were randomly assigned into two equal groups (15 patients each) via block randomization (i.e., four patients per block). They were randomized at a ratio of 1:1 to receive either rifampin (group 1) or matched placebo capsules containing inert starch (group 2). All the examiners and investigators were masked to the treatment groups. The rifampin group received a single daily dose of 600 mg of rifampin (Alhavi Pharma Co., Iran) or 300 mg in cases wherein a subject's body weight was less than 50 kg, whereas the placebo group received placebo capsules once a day (Alhavi Pharma Co., Iran). The medications were administered for 30 days. Before the initiation of the treatment, the liver function, serum creatinine, complete blood count, platelet count, and 8 A.M. serum cortisol (C_{8AM}) of the patients were assessed. The measurement of C_{8AM} was repeated at months one and two. At baseline (one day before intervention), complete ophthalmic examination, including the logarithm of the minimum angle of resolution (logMAR) BCVA, was performed on all the cases. To establish the presence of SRD or PED, all the subjects were evaluated via FA and spectral-domain optical coherence tomography (SD-OCT) (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany). SRD or PED height was measured using SD-OCT, wherein the calipers of the Spectralis device were positioned manually, and the scan with the highest detachment was used. If the SRD and

PED overlapped on the OCT, the heights of both detachments were incorporated into the exam; otherwise, the highest detachment was selected for evaluation [24]. Follow-up visits were performed every month after the baseline assessment; all in all, the intervention lasted for three months. At each follow-up visit session, a full ophthalmic assessment, involving logMAR BCVA measurement and SD-OCT assessment of the macular area, was carried out for all the subjects.

Patients who did not appear for evaluation at the appointed time or did not tolerate or showed signs of sensitivity to the medicines were excluded from the study. The primary outcomes for analysis were BCVA and SRD height, and the secondary outcome was serum cortisol. All the data were recorded on a checklist and used for comparison between the groups.

Statistical analysis

After data collection, the data on the checklist was inputted into the Statistical Package for the Social Sciences (SPSS) for Windows version 17.0 (IBM Corp., Armonk, NY). SPSS was also used for all the statistical analyses performed in this study. Before statistical analysis, data normality was verified through the Kolmogorov–Smirnov test. Paired *t*-tests were conducted to examine VA, retinal detachment height, quantitative variations in serum cortisol, and group separation. An independent *t*-test was carried out to compare the variations in means between the groups. To compare the trends of changes in variables, repeated-measures analysis of variance with Greenhouse–Geisser correction was implemented. All the tests were of two-tailed form, and a *P*-value less than 0.05 was considered statistically significant.

Results and Discussion

Among the 30 patients, 27 (14 in the rifampin group and 13 in the placebo group) completed the study. None of the patients refused the treatment because of rifampin's side effects, but three patients were lost to follow-up; one patient from the intervention group and two from the control did not return for their follow-up evaluation and were thus excluded from the analysis **(Figure 1)**.

Among the patients, 22 (73.3%) were male and 8 (26.7%) were female, with a mean±SD age of 35±7 years (range: 25–50). The two groups were matched concerning baseline demographic and clinical characteristics **(Table 1)**. No difference existed between them as to gender distribution (P = 0.999) and mean age (P = 0.508).

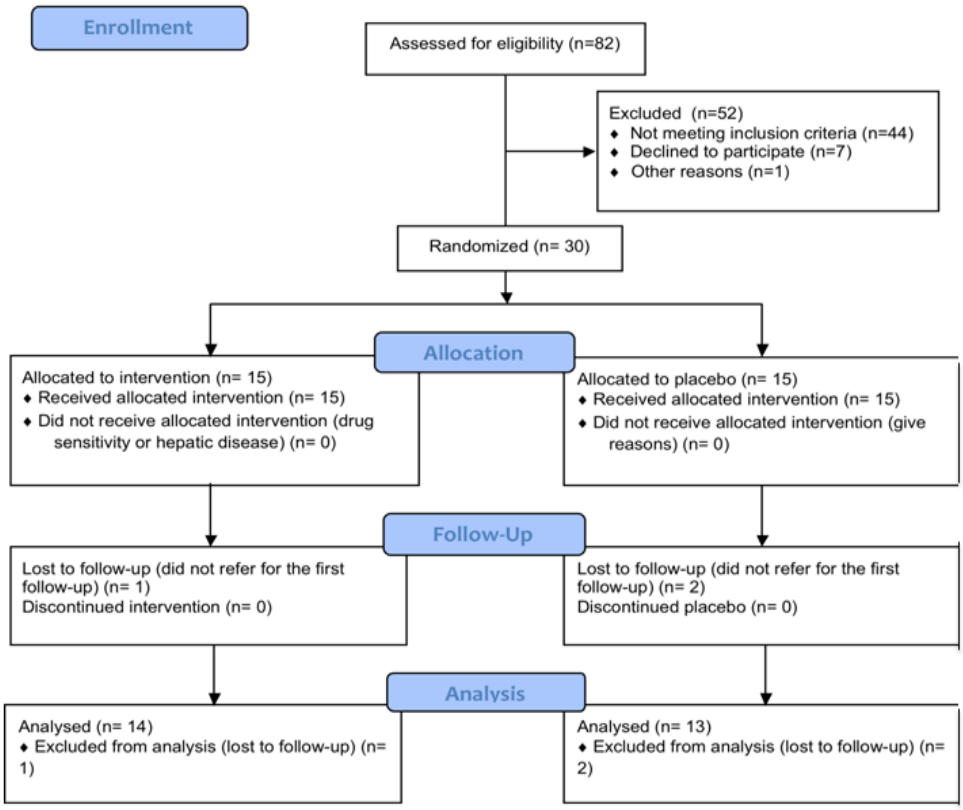

Figure 1. Patient Enrollment Chart

Table 1. Demographic and Baseline Characteristics of Patients in Rifampin and Placebo Groups

Characteristics	Rifampin (n = 15)	Placebo (n = 15)	*P*
Age (y), mean (SD)	35.8 (7.3)	36.4 (7.1)	0.51
Male sex, n (%)	11 (73.3)	11 (73.3)	0.99

Mean BCVA, logMAR (SD)	0.28(0.24)	0.27 (0.20)	0.93
Retinal detachment height (µm), mean (SD)	257.1(120.3)	264.4(154.2)	0.89
Serum cortisol 8 AM (mg/dl), mean (SD)	14.5(8.7)	15.1(5.8)	0.81

SD=standard deviation; logMAR=logarithm of minimum angle of resolution

A significant mean improvement in the BCVA of both groups was found at one, two, and three months after the intervention. Despite this significance in improvement, however, the difference between the groups was not statistically significant at any point of the treatment (P > 0.05) **(Table 2)**. The mean height of retinal detachment significantly decreased in each group at the first, second, and third-month follow-ups, but the difference between the groups was not statistically significant (P > 0.05) **(Table 2)**. **Figures 2 and 3** show that the trends of changes in BCVA and retinal detachment height in the groups were comparable (P = 0.65 and P = 0.76 for the rifampin and placebo groups, respectively).

Table 2. Changes in Visual Acuity and Retinal Detachment Height at Baseline, 1, 2, and 3 Months

	Baseline	1 Month	2 Months	3 Months
Mean BCVA, LogMAR (SD)				
Rifampin	0.28(0.24)	0.17(0.14)	0.12(0.11)	0.04(0.05)
Placebo	0.27(0.20)	0.19(0.16)	0.16(0.18)	0.10(0.15)
P value	0.93	0.76	0.58	0.17
Retinal detachment height (µm), mean (SD)				
Rifampin	257.1(120.3)	146.3(90.2)	82.2(90.7)	44.4(60.5)
Placebo	264.4(154.2)	171.0(143.2)	91.0(116.2)	52.1(73.8)
P value	0.89	0.60	0.83	0.77

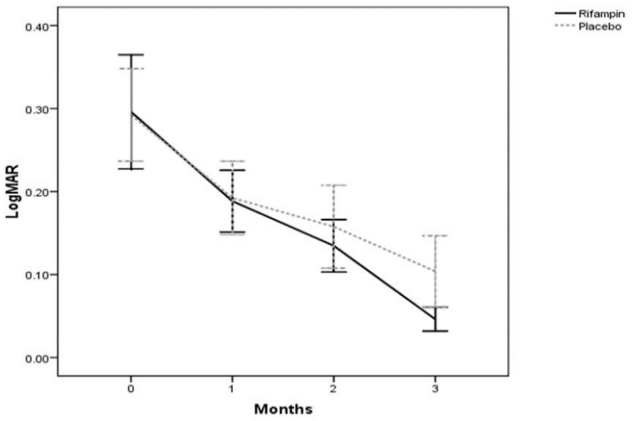

Figure 2. Monthly Change in Visual Acuity in Both Groups. Mean Values with SE Bars Are Shown for Each Time Point.

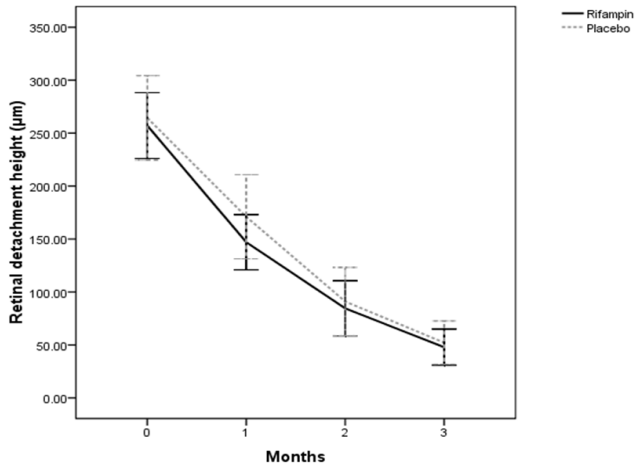

Figure 3. Monthly Change in Retinal Detachment Height in Both Groups. Mean Values with SE bars Are Shown for Each Time Point.

At baseline, the groups did not statistically differ as regards the mean C_{8AM} (P = 0.81). At month 1, however, a significant difference in this measure was found between the groups (P = 0.03). Nevertheless, the difference at the end of the second month was not statistically significant (P = 0.06). **Table 3** shows the C_{8AM} of the groups at baseline and the changes in this variable at one and two months after the initiation of the treatment.

Table 3. Changes in Serum Cortisol Level at 1 and 2 Months

	Baseline	1 Month	2 Months
Serum cortisol level*, mean (SD)			
Rifampin	14.4(8.6)	11.2(6.51)	12.4(6.1)
Placebo	15.1(5.8)	15.8(3.3)	16.5(4.1)
P value	0.81	0.03	0.06

*Serum cortisol level at 8 A.M. (mg/dl)

The initial hypothesis of this study was that rifampin exerts an anti-glucocorticoid effect on CSC, as indicated as well in previous experiments on this condition [19-22]. To verify this supposition, we selected 30 patients with acute CSC and randomized them into intervention and placebo groups. The results showed that the administration of oral rifampin at the described dose and duration of treatment had no effect that surpasses that of the placebo on the treatment of acute CSC.

The effects of exogenous steroids on the development and exacerbation of CSC and the elevated glucocorticosteroid levels of CSC patients suggest that excessive glucocorticoid effects are implicated in the pathogenesis of CSC [32]. This possibility motivated researchers to study the influence of medications with anti-steroidal properties on the disease. One such drug is ketoconazole, an anti-fungal agent with additional anti-glucocorticoid effects that was believed to be a rational option as medication. Esfahani *et al.* indicated that administering 400 mg of ketoconazole per day completely or partially eliminated central macular thickness and BCVA in some of the patients in a study involving 12 acute CSC and seven chronic CSC subjects [33]. Contrastingly, Golshahi *et al.* found that a month-long administration of 200 mg ketoconazole per day did not surpass the effects of placebo treatment [24]. A few studies reported resolution of the subretinal fluid in patients with CSC following the administration of oral rifampin [27-29]. Rifampin is a cytochrome P450 and 3A4 inducer and thus increases the processing of endogenous steroids through the induction of hepatic metabolism [34, 35]. It was considered an off-label treatment after the alleviation of chronic CSC was observed in a patient who was on multi-drug antibiotic therapy for presumed latent tuberculosis, which was an effect that persisted on rifampin monotherapy [26].

Despite these positive outcomes, the exact role of corticosteroids in CSC pathogenesis is inadequately understood. Late research evaluated mineralocorticoid receptors in choroidal tissue and hypothesized that glucocorticoids activate mineralocorticoid receptors and cause or aggravate CSC manifestations [31]. Khan *et al.* investigated 31 patients with idiopathic CSC to ascertain the efficacy of administering 300 mg of rifampicin for three months and reported improved BCVA and reduced central macular thickness after a month [23]. However, the authors did not include a control group for comparison that demonstrates the pure effects of rifampin on CSC. In another case series, Steinle *et al.* discovered a favorable effect of 600 mg/day of rifampin on patients with chronic CSC [36]. The drawback to this study is that it also neglected to include a control group for result comparison, thereby preventing a definitive conclusion as to whether the observed efficacy was related to the intervention. Nelson *et al.* recounted that 600 mg of rifampin daily cured CSC by inducing the catabolism of endogenous steroids, but this dose has been related to complications such as hepatotoxicity [37].

In one non-comparative interventional case series, all the patients were treated with 600 mg of rifampin per day and subjected to follow-ups for eight to 12 weeks. The mean changes in central macular thickness from the baseline were –99 μm (SD±167) at week 1, –102 μm (SD±215) at week 8, and –93 μm (SD±91) at week 12. Three patients gained zero lines of vision, and two gained ≥3 lines of vision. According to the researchers, the acute cases responded more favorably to the treatment. Note that the patients' serum or urine cortisol levels were not measured [27].

The results of our prospective randomized clinical trial showed that a month-long administration of oral rifampin was not more advantageous than placebo treatment in the improvement of BCVA or the resolution of subretinal fluid in patients suffering from acute CSC. Our findings contrast with those of the aforementioned reports, indicating the benefit of oral rifampin in treating the disease. This inconsistency may be attributed to the absence of control groups and randomization in the previous studies, patient composition in the current research (only acute CSC cases), and the relatively shorter duration of rifampicin treatment in the previous works (one month). In the present study, a significant improvement in VA and the absorption of subretinal fluids were observed in both groups during the follow-up sessions at months 1 to 3. As explained earlier, however, the difference between the groups was not statistically significant at any point of the treatment. Similar to previous studies, the current research used a rifampin dose of 600 mg. The statistically significant decrease in serum cortisol after one month of medication in the treatment group favored the use of an adequate dose of rifampin. Rifampin doses as low as 300 mg daily induce the hepatic metabolism of endogenous and exogenous glucocorticoids within several days of treatment [38, 39].

In a recent case report, the authors described a scarce case of a 44-year-old Asian man with acute CSC, whose endocrinology assessment indicated hypothalamic-pituitary-adrenal axis suppression with low serum cortisol and the existence of

pituitary microadenoma. He was treated with systemic eplerenone and hydrocortisone. After 12 weeks, bullous detachment was fully resolved. The uniqueness of this case originates from the fact that it is, thus far, the only acute CSC case with underlying low serum cortisol that responded to a mineralocorticoid antagonist [40]. It emphasizes different endocrine abnormalities other than elevated serum cortisol that can happen in patients suffering from CSC.

Emerging evidence has also implicated the mineralocorticoid receptor pathway in the pathogenesis of CSC and has sparked interest in the use of mineralocorticoid receptor antagonists as a potentially viable treatment option for the disease. A prospective randomized, double-blind, placebo-control study suggested that oral eplerenone (a blocker of aldosterone binding at the mineralocorticoid receptor) therapy is safe and potentially effective in treating chronic CSC with persistent subretinal fluid [29]. In another prospective interventional case series, for eyes with persistent SRF due to CSC, spironolactone treatment was related to a statistically significant reduction in SRF height and betterment in BCVA [30].

A meta-analysis of interventions into CSC noted that although acute CSC treatment may be unnecessary (as it often may be self-limiting), its management is typically guided by an individual's needs and natural history [41]. Correspondingly, most patients who are in the active phase of their lives demand faster recovery options, thus underscoring the need for detailed studies of novel treatment approaches.

The limitations of this work are worth noting. First, the study involved a small sample; a larger one can be essential to discover significant treatment impacts. Second, the sample lacks patients with increased baseline serum or urine cortisol levels; thus, whether the same results will be derived in the presence of patients with hypercortisolism is unclear. Third, the sample did not include patients with recurrent or chronic CSC; further comparative studies are required to determine the effectiveness of this form of treatment in a range of patients with varied disease etiologies and severities. Fourth, several risk factors have been related to the formation of CSC, including psychological factors, such as type A personality and life-related stress, which were not controlled for in this study; such issues can act as confounding variables. Finally, measuring cortisol levels based on a 24-hour urine sample would have ensured more accurate results; however, this method was infeasible because of poor patient collaboration.

Conclusion

In sum, numerous studies have demonstrated the role of rifampin in chronic CSC, but no study has probed into the effects of this drug on acute CSC. To the best of our knowledge, this randomized clinical trial is the first to examine the efficacy of rifampin in treating the acute form of the disease.

The overall evidence indicated that taking oral rifampin for one month has no more impact on the improvement of VA or the resolution of subretinal fluid in acute CSC patients. Beyond a month of treatment, however, the medication reduced endogenous steroids levels. Nevertheless, after drug cessation, this effect on serum cortisol disappeared. Future studies that control for the confounding effects of other risk factors should be conducted to illustrate the pure effects of rifampin or other newer mineralocorticoid antagonists on acute CSC.

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Ethics statement: The ethics committee of Guilan University of Medical Science approved this study.

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