

Therapeutic Effects of Low Dose Acetylsalicylic Acid on Acute Central Serous Chorioretinopathy: A Prospective, Interventional, Single Centre Case Series

Naser Samadi Aidenloo¹, Qader Motarjemizadeh², Nasim Moharramzadeh³

¹Department of Ophthalmology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Email: dr.nasersamadi@yahoo.com

²Department of Ophthalmology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Email: gmotarjemizadeh@gmail.com

³Department of Ophthalmology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Email: mohammadzade.n@gmail.com

*Corresponding Author, Department of Cardiology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Email: gmotarjemizadeh@gmail.com

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Abstract

Objective: Central serous chorioretinopathy (CSCR) is a common cause of central vision loss, primarily affecting men 20–60 years of age. This study aimed to investigate the efficacy of low-dose aspirin for the treatment of acute CSCR.

Methods: Totally 60 patients (60 eyes) with a history of acute CSC on fenofibrate were randomized into two groups: group A was treated with aspirin 100 mg per day orally for 1 month followed by 100 mg on alternate days for 5 months by evaluation of visual acuity, mean subretinal fluid vertical diameter (SFVD), Optical Coherence Tomography (OCT), and central macular thickness (CMT) at baseline and follow up period. Group B received no medication and was considered as the control group. Follow-up times were the first week, 1, 2, 3 and 6 months after treatment initiation.

Results: No differences were seen between the studied groups in terms of baseline BCVA ($P = 0.968$) and baseline SFVD ($P = 0.774$). BCVA improved, and SFVD was reduced significantly in the group A at all follow-up intervals compared with baseline values. Aspirin intervention (group A), compared with no intervention group (group B), was statistically more effective in improving BCVA ($P < 0.001$) and in reducing SFVD ($P < 0.001$) after 6 months. While 93.3% ($n=28$) of Group A's cases had no recurrences during the follow-up period, only 60.0% ($n=18$) of patients in the group B had a resolution of CSCR with no recurrences.

Conclusion: More rapid visual rehabilitation with fewer recurrences of CSCR were detected in the group A than in group B. These results demonstrated that orally administered aspirin may be a promising option for selected patients in the treatment of acute CSCR.



Introduction

Central serous chorioretinopathy (CSCR) is characterized by accumulation of transparent fluid at the posterior pole of the fundus [1]. There are two main types of CSC. 2 Acute CSC causes an acute localized detachment of the retina with mild to moderate loss of visual acuity associated with one or a few focal leaks seen during fluorescein angiography (FA). Chronic CSC has widespread alteration of pigmentation of the retinal pigment epithelium (RPE) related to long-term presence of shallow subretinal fluid (SRF) for >6 months.

Fortunately, CSCR is self-limiting, and the posterior pole neurosensory retinal detachment (SRD) typically resolves spontaneously. Visual acuity improvements over a relatively short time (i.e., weeks to a few months) generally accompany resolution of SRD [2–5]. Although CSCR is usually described as a benign, self-limiting disease, some cases can recur, and these often result in progressive vision loss [4–6]. Thus, early interventions should be considered in CSCR patients, before disruption of the retinal layers occurs. If SRD resolution occurs within 4 months of symptom onset, it is possible to reduce the incidence of retinal atrophy and the subsequent decrease in visual acuity [6, 7].

Treatment of CSCR has largely targeted either the RPE or the choroid, but treatment efficacy has been difficult to demonstrate. Several treatment options have been evaluated, including observation, corticosteroid discontinuation, laser therapy (e.g., photodynamic therapy [PDT], selective retinal therapy [SRT], and standard laser photocoagulation), intravitreal antivascular endothelial growth factor (VEGF) therapy, and systemic medications (e.g., carbonic anhydrase inhibitors, β -blockers, and aldosterone antagonists). However, none of these treatments are considered the gold standard, although some have better evidence of efficacy than others [8].

The literature suggests that in all types of CSCR, plasminogen activator inhibitor 1 (PAI-1) was increased [9–16]. In addition, Sogutlu et al. demonstrated that elevated levels of PAI 1 were found in patients with CSCR [17]. In light of this association of elevated levels of PAI 1 and CSRC, we decided to treat patients affected by CSCR with low-dosage Aspirin 100 mg as this antiplatelet medication is effective in decreasing the PAI-1 levels by reducing its release from platelets [18, 19].

Materials and Methods

Sixty patients with active classic or multifocal CSCR were recruited to this single blinded interventional case series at Imam Khomeini hospital (A major university hospital in Urmia, Iran), from March 2017 to March 2018. Investigation protocol underwent technical and ethical review and was approved by Ethics Committee of Urmia University of Medical Sciences. All subjects were informed about the study's objectives and only those who provided an informed consent were included in the current investigation. The study was performed in accordance with the Declaration of Helsinki and subsequent revisions.

Patients were given complete ocular examinations, including visual acuity measurement using the Early Treatment Diabetic Retinopathy Study Chart, optical coherence tomography (OCT) (Stratus OCT3, Carl Zeiss, Dublin, CA), and measurements of central macular thickness (CMT) at baseline and at follow-up. OCT images were obtained from each affected eye after pupil dilation by the same trained operator using the OCT3 system. Central macular thickness was assessed by manually measuring the distance between the vitreoretinal surface and the RPE at the foveal center. After reviewing OCT results independently, two authors (N. SA and Q.M) discussed and reached a consensus on the results. Patient information including visual acuity, SFVD, and patient group allocations were masked during the evaluation [20].

Exclusion criteria were previous medical treatment for CSCR, other ocular or retinal disease, history of coagulation abnormalities or bleeding diathesis, previous laser retinal photocoagulation, previous aspirin therapy, history of ulcerative gastric disease, pregnancy, asthma, diabetic mellitus, or allergy to aspirin. A complete ophthalmic examination was undertaken at admission in all patients, using OCT. OCT was also performed at 1 week, 1 month, 2, 3 and 6 months. Best corrected visual acuity (BCVA) measurement with Early Treatment Diabetic Retinopathy Study (ETDRS) chart was determined at every follow-up visit. All patients in the group A (n=30) were prescribed aspirin 100 mg once daily for the first month and on alternate days for the following 5 months. The prospective case series undergoing treatment (Group A), was compared with the group B as the control group consisting of 30 patients with

either classic or multifocal CSCR. Patients in Group B had complete ocular examinations at the same intervals as Group A. Primary endpoints were BCVA, SFVD and number of recurrences. Demographic characteristics, medical, surgical, and ocular history of participants were extracted from their medical records [20].

Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS ver. 17). Two-sided P values less than 0.05 was considered statistically significant for all analyses. Chi square test was used to compare qualitative variables. Changes relative to baseline in visual acuity and SFVD were evaluated by Wilcoxon signed-

rank test within the investigated groups. Analysis of covariance (ANCOVA) was employed to compare SFVD and BCVA between the two groups.

Results

This study was conducted on 60 eyes of 60 patients, randomly distributed in 3 groups each with 20 subjects. Altogether, 31 men (Aged 28-55 years; mean 38.97 ± 8.00) and 29 women (aged 29-52; mean 40.03 ± 6.99) were included to the study. The clinical and demographic characteristics of the participants are shown in Table 1. No statistically significant differences were observed between the 2 groups in terms of sex, age, number of bilateral disease, frequency of unilateral and bilateral multifocal CSCR, pre-operative BCVA, and pre-operative SFVD.

Table 1. Baseline and demographic characteristics of the study groups.

Item	Group A (n=30)	Group B (n=30)
Age (years), mean \pm SD	42.2 \pm 8.1	38.8 \pm 7.6
Sex, n (Male/Female)	17/13	14/16
Bilateral disease (%)	2 (6.7)	3 (10.0)
Multifocal CSCR, n (%)		
unilateral	2 (6.7)	1 (3.3)
bilateral	2 (6.7)	2 (6.7)
BCVA (Letters), mean (SD)	68.1 (15.1)	69.2 (16.2)
SFVD (μ m), mean (SD)	141.9 (70.8)	131.5 (71.4)

Abbreviations: BCVA: Best-corrected visual acuity; SD: Standard deviation; SFVD: subretinal fluid vertical diameter.

Compared with baseline, mean changes in BCVA were statistically significant in group A at all follow-up points (Table 2). On the other hand, no significant difference was observed in group B regarding BCVA changes from baseline at the first week as well as at months 1, 2 and 3. Average BCVA improved marginally in group B at month 6 in comparison to the baseline values (Table 2). The average BCVA was significantly higher in group A compared with group B at all follow-up visits. This difference remained significant even after adjustments for age and baseline BCVA. At the end of the follow-up period, Group A maintained a far better BVCA than Group B. Indeed, average BCVA improved by 12.2 letters in group A and 6.0 letters in the group B after

6 months. This difference remained significant even after adjustments for age and baseline BCVA (Table 2).

There was a statistically significant reduction in SFVD at all follow-up sessions compared to baseline values in the patients allocated to the group A. (Table 2). No significant difference was observed in group B in terms of SFVD changes during the first two follow up months when compared with the baseline values. Compared with baseline, mean changes in SFVD were marginally significant in group B at month 3 (Table 2). This difference remained significant even after 6 months. SFVD reduction was statistically more pronounced in group A than the group B at all follow-up assessments (Table 2).

Table 2. Within and between group comparison of BCVA and CMT values at different time points

	Group A, mean (SD)	P (within group A)*	Group B, mean (SD)	P (within group B)*	P (between group A vs. B)†
BCVA (Letters)					
Baseline	68.1 (15.1)		69.2 (16.2)		
Week 1	71.9 (15.4)	0.041	69.9 (15.5)	0.656	0.041
Month 1	73.7 (16.1)	0.011	71.3 (15.8)	0.292	0.032
Month 2	76.8 (16.9)	0.001	72.2 (15.9)	0.141	0.014
Month 3	78.9 (16.6)	<0.001	73.0 (17.1)	0.091	0.003
Month 6	79.3 (17.0)	<0.001	75.2 (16.9)	0.046	<0.001
SFVD (μm)					
Baseline	141.9 (70.8)		131.5 (71.4)		
Week 1	115.5 (53.6)	0.025	120.3 (69.8)	0.710	0.041
Month 1	99.8 (47.2)	0.007	112.6 (57.9)	0.445	0.029
Month 2	75.9 (37.9)	<0.001	117.4 (42.3)	0.070	0.008
Month 3	64.3 (29.8)	<0.001	111.3 (35.8)	0.051	<0.001
Month 6	45.5 (24.7)	<0.001	98.6 (27.5)	0.029	<0.001

*Computed by Wilcoxon signed-rank test T.

†Computed by ANCOVA adjusted for age and baseline values of BCVA/SFVD.

Abbreviations: BCVA: Best-corrected visual acuity; SD: Standard deviation; SFVD: subretinal fluid vertical diameter.

As shown in Table 3, 93.3% (n=28) of Group A had no recurrences during follow-up and 6.7% (n=2) experienced 1–3 relapses of disease. No eye showed a persistence of CSCR in aspirin treated patients (group A). In Group B, 60.0% (n=18) had a resolution of CSCR with no recurrences, 26.7% (n=8) had 1–3 further episodes of CSCR, and 13.3% (n=4) had persistence of disease.

Table 3. Number of recurrences in the investigated groups

Recurrences		Group A (%)	Group B (%)
0		28 (93.3)	18 (60.0)
≥1-3		2 (6.7)	8 (26.7)
Persistence of disease		0	4 (13.3)

Discussion

Central serous chorioretinopathy (CSCR) is an acquired chorioretinal disorder that was first described by Von Graefe in 1866 as recurrent central syphilitic retinitis [21]. Other names used to describe this disease entity include capillarospastic central retinitis, central angiospastic

retinopathy, central serous retinopathy, and central serous pigment epitheliopathy [22, 23].

Patients with CSCR most commonly complain of metamorphopsia, micropsia, blurred vision, and mild dyschromatopsia in the affected eye. On fundus examination, typical signs include a round well-demarcated detachment of the neurosensory retina at the macula. Pigment epithelial detachment (PED) of variable size can also occur and can be single or multiple. The subretinal fluid (SRF) can be clear or turbid/fibrinous. The turbid fluid may even form in the subretinal pigment epithelial (sub-RPE) space [24, 25]. In chronic CSCR or in patients with old resolved disease, RPE mottling, atrophy, and clumping might be observed [26–28]. In addition, yellow dots that are thought to represent phagocytosed photoreceptor outer segments are frequently seen just over the inner surface of the RPE [29]. Other atypical CSCR presentations include bullous neurosensory retinal detachment, inferior neurosensory detachment with atrophic tracts, and multifocal CSCR [30, 31].

CSCR is a self-limiting disease and the central vision of about 70% of patients can be recovered in 3 to 6 months. Without early treatment, long-term macular edema will damage visual function in some patients, which ultimately

leads to degeneration of visual cells. The exact cause of CSCR is not yet fully understood, but various studies have shown that it might be associated with corticosteroids, alcohol intake, or decreased function of the immune system. Although the pathogenesis of CSCR was not clear, some studies have reported that damage to the RPE could cause damage to the zonula occludens and breakdown of the RPE barrier. However, other studies have reported that choroidal circulation disorder causes damage to the RPE. In addition, elevated serum cholesterol leads to macular edema and hard exudation, which is associated with the development and severity of CSCR. More specifically, an elevation in triglycerides is associated with macular edema and hard exudation.

Drugs which improve blood circulation and glucocorticoid antagonists have been the traditional treatments for this disease. However, these types of drug have the potential to worsen symptoms, cause interlayer effusion, recurrence, and/or visual distortion for patients with retinal macular edema. This poses a serious threat to visual acuity. Laser photocoagulation and photodynamic therapy (PDT) treatment only stop the RPE leakage using laser thermal effects, but they do not reduce the abnormal choroidal blood flow. They also have the potential to elicit non-selective coagulation necrosis on tissue adjacent to the lesion area, which would result in several adverse effects, such as the formation of central scotoma, the reduction in contrast sensitivity, and secondary choroidal neovascularization (CNV). There are only a few studies on anti-VEGF treatment for CSCR, therefore, large-scale multicenter clinically controlled trials are necessary to evaluate the efficacy and safety of anti-VEGF therapy for CSCR. In addition, vitrectomy is ineffective for CSCR. Thus, furthering the understanding of the mechanism of angiogenesis, making breakthroughs on possible treatments, and discovering new drugs and key therapeutic targets to prevent CSCR have become the focus of current ophthalmic research.

Administration of aspirin enabled a more rapid recovery of the BCVA letters, more pronounced reduction in SFVD and a smaller percentage of recurrences in comparison with the control group. The number of recurrences in the group treated with aspirin was also lower in comparison with previous studies concerning the long follow-up term of CSCR [31-34]. Patients affected with the multifocal form have

shown a limited benefit of therapy, although improvement in visual acuity was found. None of the patients manifested adverse reactions to aspirin. A gastrointestinal risk exists, but appears to be dose-dependent. Even at low dosage, an increased gastrointestinal risk has been found [35], but has been very low (3%), consisting of bleeding ulcers. In our series this did not occur, probably because of the young age of our patients, their lack of history of ulcerative gastric disease, and the total number of patients included being too small to show such a rare complication.

Aspirin is a non-steroidal anti-inflammatory drug. Its main role is as an antipyretic, analgesic, anti-inflammatory and antirheumatic, and it inhibits platelet aggregation. Aspirin acts primarily through irreversible inhibition of cyclooxygenase-1 (cox1) and cyclooxygenase-2 (cox2), which prompts the decline in prostaglandin (PG) expression [36]. The DAMAD research team has administered aspirin to patients with diabetic retinopathy for more than 3 years, and has found that it can alleviate the majority of cases of retinopathy [37]. In a diabetic rat model, Lorenzini *et al* [38] observed that a low concentration of aspirin can delay the progression of diabetic retinopathy. Later studies also showed that aspirin can prevent diabetic retinopathy [39, 40]. Nowak *et al* [41] found that aspirin helps in the early treatment of AMD, whereas other studies have shown that long-term use of aspirin can lead to AMD, or that there was no clear correlation between the two [42, 43]. Whether aspirin can be used in AMD requires more evidence-based trials for verification.

Conclusion

In this study median visual acuity increased after the first week of therapy with a further improvement after six months; after this period visual acuity remained stable. Low dosage of aspirin seemed to be effective in reducing SFVD in all follow-up sessions in group A. A recurrence of the disease occurred in the 6% of the patients at the end of the follow-up. Low dosage aspirin was also effective in shortening length of disease. Indeed, patients in group A had a lower frequency of relapses than those allocated to the group B. As demonstration of the self-limited nature of CSCR, we observed a spontaneous improvement of BCVA and SFVD reduction in the untreated group in the period between 3 and

6 months. In conclusion, according to the visual-gain achievement, low recurrence rates and sustainable SFVD reduction result, it seems that the administered dosage of aspirin could be a useful treatment option for CSCR. Further studies will be needed to be able to individualize the dosage and duration of administration of aspirin and to define better the role of single factors in the coagulative cascade in the onset of this multifactorial illness.

Statements and Declarations

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Competing interests:

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Urmia University of Medical sciences (No. IR.UMSU.REC.1397.207).

Consent to participate:

Informed consent was obtained from all individual participants included in the study.

Author contributions:

N S A: Conceptualization, the original draft writing, investigation, writing including reviewing and editing and investigation and formal analysis; G. M. : Conceptualization, supervision, and project administration; N M.: Conceptualization, the original draft writing, investigation, writing including reviewing and editing

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