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Research Article

A Data Compilation Analysis on the Efficacy of Different Treatment Modalities in Patients with Central Serous Chorioretinopathy (CSCR)

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Abstract

Purpose: Central serous chorioretinopathy (CSCR) is the fourth most common retinopathy that is often observed until resolution. However, treatment is warranted if subretinal fluid persists for more than 3 months. The purpose of this study is to compare the efficacy of different treatment modalities in patients with acute and chronic CSCR.

Methods: A data compilation analysis was performed by combining our IRB approved retrospective data with fourteen research papers that met the selection criteria of this review. The total number of patients that were analyzed in our study was 69 patients with acute CSCR and 155 patients with chronic CSCR.

Results: For acute CSCR, topical bromfenac and nepafenac, oral eplerenone, and subthreshold laser are significantly more effective than observation approach in resolution of subretinal fluid. All treatments, however, had a statistically similar efficacy. For chronic CSCR, eplerenone, spironolactone, and subthreshold laser only had modest effects on resolution of subretinal fluid, while half-fluence photodynamic therapy (PDT) was the most effective means of treatment that was statistically more effective than the former treatments. Bevacizumab, conventional PDT, and focal laser photocoagulation were slightly less effective than half-fluence PDT but the difference did not reach statistical significance.

Conclusion: For acute CSCR, topical bromfenac or nepafenac, oral eplerenone, and subthreshold laser have similar efficacies in resolution of subretinal fluid. For chronic CSCR, half-fluence PDT is superior to eplerenone, spironolactone, and subthreshold laser in terms of central macular thickness (CMT) and best-corrected visual acuity (BCVA) outcomes.

Keywords: *NSAIDs; Bromfenac; Nepafenac; Spironolactone; Eplerenone; Photodynamic Therapy; PDT; Micropulse Laser; Subthreshold Laser; Bevacizumab, avastin, focal laser photocoagulation*

Introduction

Central serous chorioretinopathy (CSCR or CSC) is the fourth most common retinopathy that is characterized by localized serous detachment of the neurosensory retina involving mainly the macular area. Patients with CSCR may present with blurred vision, relative central scotoma, and reduced contrast sensitivity, though, owing to its self-limiting course, acute CSCR is often observed until resolution

within 3-4 months of onset [1-3]. The chronic form of CSCR, however, can be associated with poor visual outcome owing to development of tracks of retinal pigment epithelium (RPE) atrophy, intraretinal cystoid cavity, and secondary choroidal neovascularization (CNV), as a consequence of which progression to chronic CSCR warrants treatment [4-7].

The exact etiology of CSCR remains unknown and yet, many different treatment options are available including systemic anti-corticosteroid medications, mineralocorticoid receptor antagonists, photodynamic therapy (PDT), transpupillary thermal therapy, focal laser photocoagulation, micro pulse laser, and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents [8,9]. In recent years, considering the potential complications of standard (or conventional) PDT such as visual loss, choriocapillary non-perfusion, RPE atrophy, and choroidal neovascularization, modified photodynamic therapies such as half-fluence and half-dose PDT have become more popular [10]. Nevertheless, it is not clear which of these treatment options is best suitable for treatment of chronic CSCR. In the present study, we are evaluating the efficacy of different treatment modalities for both acute and chronic CSCR, using our own unpublished data combined with available CSCR publications that have provided individual participant data on treatment outcomes. Our hope is that this comparative data analysis provides insights into criteria that justify the use of each of these treatment options for patients with different severities and durations of CSCR.

Methods

This study received IRB approval by the UHS (University Health System, San Antonio, Texas) and MCOA (Medical Center Ophthalmology Associates, San Antonio, Texas). Considering the retrospective nature of the study, patient consent was not required and the information collected had no effect on the treatment outcome. All stages of study were conducted in accordance with the principles set forth by the Declaration of Helsinki. Internet search engines such as PubMed, ScienceDirect, and Google were used to collect CSCR publications that have provided individual participant data for central macular thickness (CMT) and best corrected visual acuity (BCVA) prior and after the treatment.

Inclusion criteria included: 1) presence of subretinal fluid in the macular area confirmed with an OCT machine, and 2) no prior treatment. Acute CSCR was defined as CSCR at first presentation to eye clinic with visual symptoms of less than 3 months duration. More than 3 months duration of symptoms are considered as chronic CSCR. Exclusion criterion included: 1) the presence of choroidal neovascular membranes or ocular disorders other than CSCR, and 2) baseline CMT or BCVA that was statistically different from our own collected data. It is worth noting that none of the selected articles had a CMT or BCVA that statistically deviated from our own baseline data. For all publications, the reported BCVA was converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letter equivalents to the best of our abilities [11]. The data were then graphed using Microsoft Excel and analyzed for their statistical significance using one-way analysis of variance (ANOVA) with post hoc Tukey's test.

Results

Clinical data from our institutes combined with 14 other publications were used to analyze central macular thickness (CMT) and best corrected visual acuity (BCVA) outcomes in 69 patients with acute CSCR and 155 patients with chronic CSCR. In particular, individual participant data combination was preferably selected over aggregate data meta-analysis considering analytically more powerful nature of the former approach along with better characterization of outcomes [12].

Table 1 summarizes the results of these studies for patients with acute CSCR. For all groups, there was no statistical significance for baseline CMT ($p = 0.064$) and BCVA ($p = 0.89$). In these patients, treatment with topical bromfenac or nepafenac (1 drop 4 times a day), oral eplerenone (25 mg/day for 1 week and then 50 mg/day afterward), or subthreshold laser results in a significantly faster resolution of subretinal fluid compared to the observation group (Figure 1). Nevertheless, there was no statistical significance between any of these treatment modalities. Treatment groups had more than two to five ETDRS letter gain compared to the observation group (Figure 2) but this difference did not reach statistical significance ($p = 0.066$).

Age	# of Patients	Management	Initial CMT (µm)	Follow up CMT (µm)	Reduction in CMT (µm)	Initial BCVA	Follow up BCVA	ETDRS Letter Gain	References
48.3	25	Observation	414.7	391.9	22.8	76.7	76.9	0.2	[13-16]
47	17	Topical NSAIDs	476	291	185	75.3	80.8	5.5	[13,16]
44.3	16	Eplerenone	426.2	283.5	142.7	77.8	82.2	4.4	[13-15]
56	11	Subthreshold laser	336.3	152.8	183.5	75.5	78.3	2.8	[17]

Table 1: *Characteristics and results of different treatment modalities in patients with acute central serous chorioretinopathy (CSCR).*

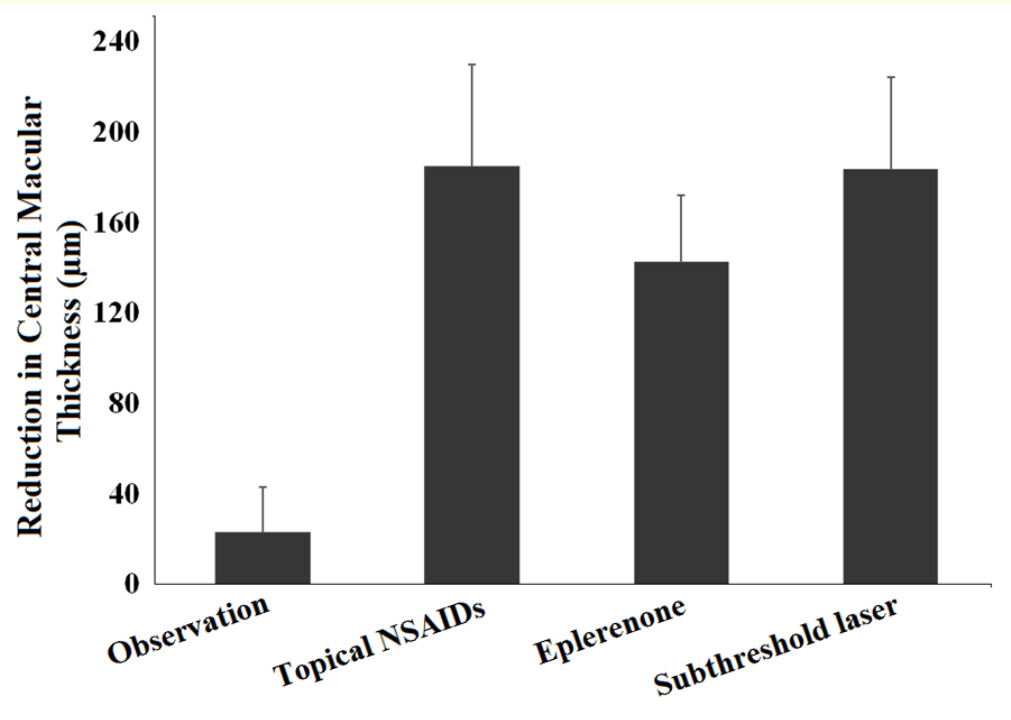

Figure 1: *Average reductions in central macular thickness (CMT) of patients with acute central serous chorioretinopathy (CSCR). In comparison to the observation group, there was a significant reduction in CMT of patients that were treated with topical nonsteroidal anti-inflammatory drugs (p = 0.002), oral eplerenone (p = 0.037), and Subthreshold laser (p = 0.009). The difference between these treatment groups, however, did not reach statistical significance [one-way analysis of variance with post hoc Tukey's test]. Error bars represent standard error of the mean.*

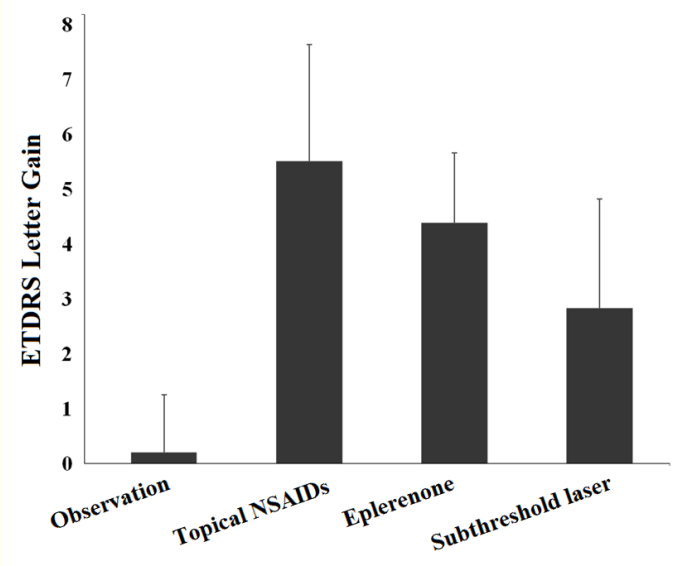

Figure 2: *Average Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain in patients with acute central serous chorioretinopathy (CSCR). Treatment groups had better visual outcomes compared to the observation group but this difference did not reach statistical significance (p = 0.066) [one-way analysis of variance]. Error bars represent standard error of the mean.*

Table 2 summarizes the results for patients with chronic CSCR, for which there was no statistical significance for baseline BCVA (p = 0.061) or CMT (p = 0.51). Spironolactone (25 to 100 mg daily), eplerenone (25 to 50 mg daily), and Subthreshold laser had a modest effect on resolution of subretinal fluid with no statistical significance between any of these groups. On the other hand, half-fluence PDT proved to be the most effective means of therapy with a statistically significant difference in resolution of subretinal fluid compared to the micropulse laser or oral mineralocorticoid receptor antagonists (Figure 3). Conventional PDT, laser photocoagulation, and bevacizumab were slightly less effective than half-fluence PDT in reduction of CMT but this difference did not reach statistical significance. Finally, ETDRS letter gain for patients that were treated with half-fluence PDT was statistically more significant than all other treatment modalities (Figure 4).

Mean Age	# of patients	Management	Initial CMT (µm)	Follow up CMT (µm)	Reduction in CMT (µm)	Initial BCVA	Follow up BCVA	ETDRS Letter Gain	References
42.8	23	Spironolactone	302.4	244.4	58	62	66.2	4.2	[13,18]
46	32	Eplerenone	349.8	273.4	76.4	70	75.8	5.8	[13,19]
43.9	26	Subthreshold laser	325.2	241.6	83.6	60.3	64.2	3.9	[17,20,21]
49.1	18	Bevacizumab	319.3	201.8	117.5	56.8	65.2	8.4	[13,22,23]
45	18	Standard PDT	342.4	202.5	139.9	57.6	67.2	9.6	[24,25]
42.2	16	Focal Laser photocoagulation	343.4	167.6	175.8	70.4	75.8	5.4	[26]
47.6	22	Half fluence PDT	377.7	166.2	211.5	60.1	79	18.9	[27]

Table 2: *Characteristics and results of different treatment modalities in patients with chronic central serous chorioretinopathy (CSCR).*

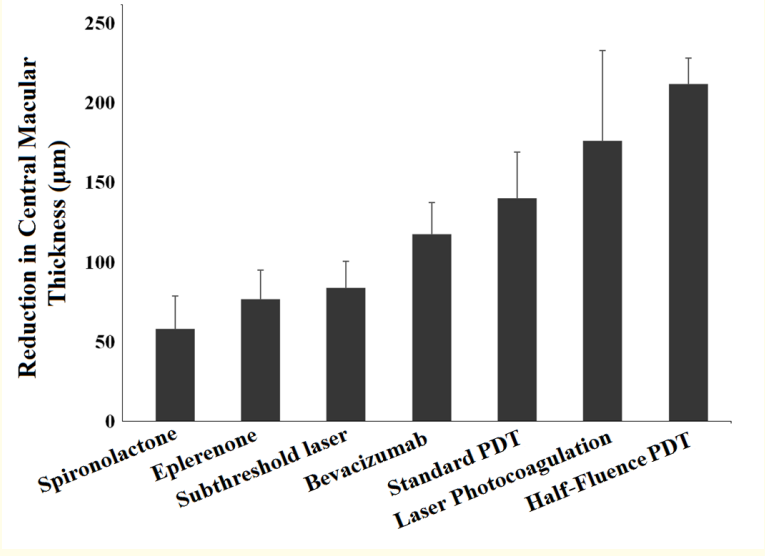

Figure 3: *Percentage reductions in central macular thickness (CMT) of patients with chronic central serous chorioretinopathy (CSCR). Patients treated with half-fluence photodynamic therapy (PDT) had a significant CMT reduction in comparison to the spironolactone (p = 0.001), eplerenone (p = 0.001) and subthreshold laser (p = 0.002) groups. Patients treated with laser photocoagulation also had a significant CMT reduction (p = 0.027) compared to the spironolactone group [one-way analysis of variance with post hoc Tukey's test]. Error bars represent standard error of the mean.*

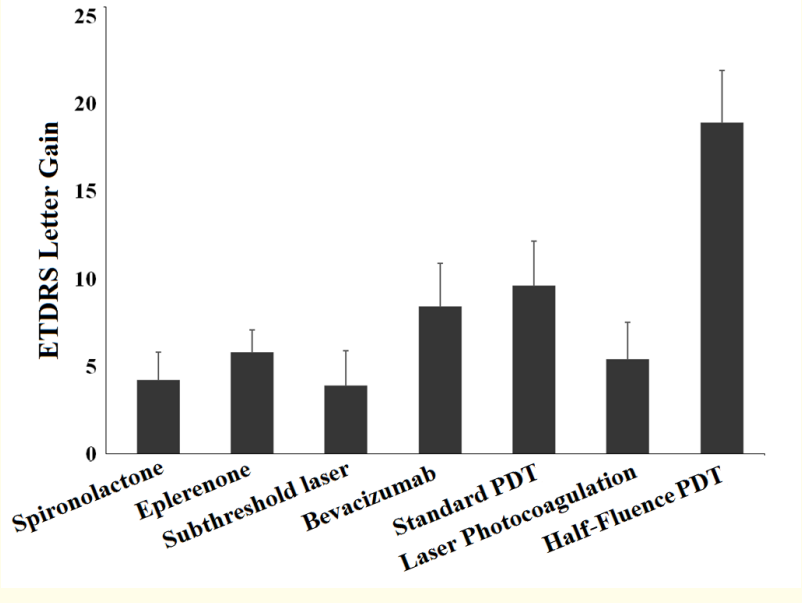

Figure 4: *Average Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain in patients with chronic central serous chorioretinopathy (CSCR). Patients treated with half-fluence photodynamic therapy (PDT) had a significant improvement in best corrected visual acuity (p<0.05) compared to the rest of treatment modalities. Otherwise there was no statistical significance between different treatment groups [one-way analysis of variance with post hoc Tukey's test]. Error bars represent standard error of the mean.*

Discussion

The exact etiology of CSCR is not known but it is thought that the mechanism of pathogenesis is attributed to increased permeability of choroidal vessels with subsequent accumulation of subretinal fluids [28]. Alternative proposed mechanisms include steroid-mediated impairment of RPE barrier function, choroidal vascular autoregulation, and hypercoagulability. In fact, steroid use and conditions that are associated with increased cortisol production (i.e. pregnancy and Cushing disease), type A personality, and psychological stress are considered as risk factors to CSCR [29,30].

Given its self-limiting nature and the role of high levels of corticosteroids in pathogenesis of CSCR, patients with the acute form are often observed until resolution while advocating lifestyle modifications and discontinuation of any steroid use. The chronic form, however, needs immediate attention owing to potential adverse effects such as RPE atrophy and choroidal neovascularization that can cause permanent loss of visual function [1-7]. Considering the multifactorial etiology of CSCR, it is also not surprising that multiple different treatment approaches are proven effective, the mechanisms for which are discussed below.

Recently we have shown that topical nonsteroidal anti-inflammatory drugs (NSAIDs) such as bromfenac and nepafenac are highly effective in treatments of patients with acute CSCR [16]. Other studies also support the role of topical bromfenac and nepafenac in promoting BCVA and CMT recovery in patients with acute CSCR [31,32]. Likewise, treatment with aspirin resulted in faster visual recovery and reduced recurrence of CSCR compared to the control group [33,34], suggesting protective nature of aspirin and other NSAIDs against this form of retinopathy. While the exact role of NSAIDs in protection against CSCR is not known, different studies suggest that their protective role may be attributed to anticoagulant properties that prevent platelet aggregation in the choriocapillaris [34], blockage of cyclooxygenase enzymes that attribute to retinal edema by production of prostaglandins [35,36], as well as decreased secretion of aldosterone, the concentration of which is positively correlated with subfoveal choroidal thickness and increased risk of CSCR [37-40].

The mechanism of aldosterone in pathogenesis of CSCR is attributed to expression of the calcium-dependent potassium channel in the endothelium of choroidal vessels with subsequent vasodilatory effects and leakage of choroidal vessels [40]. Therefore, patients with chronic CSCR are often treated with mineralocorticoid-receptor antagonist such as eplerenone and spironolactone [18,19]. An alternative therapy to acute CSCR is micropulse laser, which enables subthreshold therapy to the RPE and choroid with presumable enhanced pumping efficacy of RPE and production of anti-inflammatory cytokines that promote faster resolution of subretinal fluid [41]. The results of our study demonstrates that for acute CSCR, topical NSAIDs, oral eplerenone, and subthreshold micropulse laser have similar efficacies in resolution of subretinal fluid and enhancement of BCVA (Figures 1 and 2). In our opinion, early intervention in patients with acute CSCR mediates faster resolution of subretinal fluid and may possibly prevent chronicity compared to the observation approach, which is the current standard of care. In particular, considering the excellent safety profile of topical NSAIDs and their common use by ophthalmologists for treatment of post-operative cystoid macular edema [36], we recommend the use of topical nepafenac and bromfenac in treatment of acute CSCR. Nevertheless, additional work with larger sample sizes are needed to fully understand the role of topical NSAIDs in preventing chronicity and/or recurrence, and to also evaluate the efficacy of more commonly used topical NSAIDs such as ketorolac.

Additional therapies that are employed in patients with chronic CSCR include laser photocoagulation, photodynamic therapy, as well as off-label use of antivascular endothelial growth factor (anti-VEGF) injections. It is thought that anti-VEGF injections may help with chronic CSCR by reducing choroidal hyperpermeability, and yet, there are controversial results regarding effectiveness of bevacizumab in chronic CSCR [22,23,42-44]. Laser photocoagulation is an alternative treatment that can be applied to the RPE leakage points to induce thermal sealing effects on areas of RPE defect [26,45]. Finally, an effective means of therapy for chronic CSCR is photodynamic therapy (PDT), which induces choroidal vascular remodeling and narrowing of choriocapillaries that reduces choroidal hyperpermeability. The standard or conventional PDT is performed via intravenous infusion of 6 mg/m^2 body surface area verteporfin over 10 minutes period followed by application of 689 nm laser at energy of 50 J/cm^2, intensity of 600 mW/cm^2, and photosensitization time of 83 seconds [46,47]. Neverthe-

less, the potential side effects of standard PDT such as severe visual loss, RPE atrophy and choroidal ischemia, as well as risk of secondary choroidal neovascularization have restricted the widespread use of this technique Therefore, to avoid these adverse events, investigators have started using half-fluence, half-dose, and short-time PDT for treatment of chronic CSCR [10,25,48]. The results of our study demonstrates that for chronic CSCR, half-fluence PDT provides superior CMT outcomes to micropulse laser and oral mineralocorticoid antagonists (Figure 3). Likewise, half-fluence PDT had superior BCVA outcomes to other treatment modalities such as bevacizumab, focal laser photocoagulation, and standard PDT. These results suggest that for more severe forms of chronic CSCR with significant increase in CMT, treatment with half-fluence PDT is a more reasonable approach than micropulse laser, eplerenone, or spironolactone. Laser photocoagulation and anti-VEGF injections are alternative options, though caution must be exercised with the use of bevacizumab considering controversial reports of its effectiveness.

It is worth noting that our individual participant data compilation approach provides a powerful tool for comparison of different treatment modalities and yet, given the lack of data sharing and inaccessibility to individual participant data for majority of studies, we were unable to include other treatment modalities in our comparison study. For instance, while our study demonstrates the superiority of half-fluence PDT to other treatment modalities in terms of BCVA and/or CMT outcomes, there is literature evidence that suggests a high recurrence rate of patients that are treated with half-fluence PDT. These studies demonstrate that half-fluence PDT has a higher rate of recurrence in comparison to half-dose PDT, while the latter treatment has induced a more rapid reabsorption of the subretinal fluid with an equal safety profile to half-fluence PDT [49,50]. Therefore, while half-fluence PDT provides a very promising outcomes in comparison to other treatment options, further investigation needs to be done to directly compare the efficacy of this treatment with other forms of modified PDT such as half-dose and short-time PDTs.

Conclusions

Topical bromfenac or nepafenac, oral eplerenone, and subthreshold laser have similar efficacies in resolution of subretinal fluid in patients with acute CSCR. For chronic CSCR, half-fluence PDT is superior to eplerenone, spironolactone, and subthreshold laser in terms of CMT and BCVA outcomes and thus, the former treatment may be better suited for treatment of patients with significant build-up of subretinal fluid.

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