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Original Article

Ophthalmology Section

Efficacy and Safety of Oral Eplerenone in Acute Central Serous Chorioretinopathy: A Randomised Controlled Study

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ABSTRACT

Introduction: Acute Central Serous Chorioretinopathy (CSCR) is an important form of acquired maculopathy that usually presents as localised serous detachment of the neurosensory retina. Although, the disease is typically self limiting over a period of 2-3months, a percentage of patients ultimately develop chronic RPE changes. Eplerenone, a potential Mineralocorticoid Receptor (MR) antagonist, may play a role in regulating choroidal vascularity and modifying the disease in chronic CSCR.

Aim: To assess the safety and efficacy of oral eplerenone medication in acute CSCR.

Materials and Methods: This was a randomised controlled trial that included 162 eyes of 162 patients with acute CSCR. Patients were divided into two groups– Group-A, which received oral Eplerenone, and Group-B, which received Placebo therapy. Each group comprised 81 eyes. Best Corrected Visual Acuity (BCVA), Central Macular Thickness (CMT), and serum potassium (K+) levels were measured at baseline and monthly intervals for three consecutive months. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Statistics version 20 software (IBM Corp., Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant.

Results: The differences in CMT in Group-A and Group-B were 279±56.41µm and 207±68.88 µm ($p<0.01$) at the end of the first month and 361±33.56 µm and 278±46.27 µm at three months ($p<0.01$), respectively. The average BCVA improvement in Group-A and Group-B was 6.05 lines and 4.21 LogMAR lines, respectively, at the conclusion ($p=0.002$). Deterioration to chronicity was seen in 3.7% of the eyes in Group A and 17.3% of the eyes in Group B. The increase in Serum K+ at three months was 0.61±0.27 mg/dL in Group-A and 0.1±0.21 mg/dL in Group-B ($p=0.03$).

Conclusion: Eplerenone is a safe and effective first-line treatment option for acute CSCR, leading to faster and higher resolution with protection from progression to chronicity.

Keywords: Central macular thickness, Serum potassium, Spectral domain optical coherence tomography

INTRODUCTION

The CSCR is defined as serous retinal detachment and/or RPE detachment, where changes most often are confined to the macula and associated with leakage of fluid through the RPE into the subretinal space [1,2]. It is the fourth most common non-surgical exudative retinopathy after age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion [3]. It affects Asian and Caucasian populations more commonly than other ethnicities [4].

Acute CSCR predominantly affects males, and the incidence among middle-aged adults is the highest [5]. It is typically an innocuous retinopathy that resolves spontaneously in 2 to 3 months [2,6]. Patients with documented Sub-Retinal Fluid (SRF), with or without RPE detachment on OCT, and with persistent or progressive visual symptoms for more than three months were considered as chronic CSCR in an earlier study [7]. Previous literature suggests that 15% of acute cases may progress to chronic CSCR, causing irreversible damage to the photoreceptors and resulting in subnormal visual gain [8,9]. Therefore, considering that young adults have the highest incidence, a rapid, safe, and efficient method of treatment is required for acute CSCR.

The multifactorial pathogenesis of CSCR is complex and involves choroidal vascular dysregulation, which has been recently blamed for its occurrence [10]. This is confirmed by the choroidal hyperpermeability changes shown by fluorescein angiography and/or indocyanine green angiography [10]. New insights into the pathogenesis have revealed that glucocorticoid and mineralocorticoid dysfunction also significantly contribute to the pathogenesis [9]. In animal models, choroidal MR activation prompted choroidal vasodilation and subsequent leakage, while MR antagonism nullified the effect [9]. This has led to investigations regarding the utility of mineralocorticoid antagonists as a potential medication for treating CSCR, particularly eplerenone, which was found to be free from significant anti-testosterone side-effects [4,11].

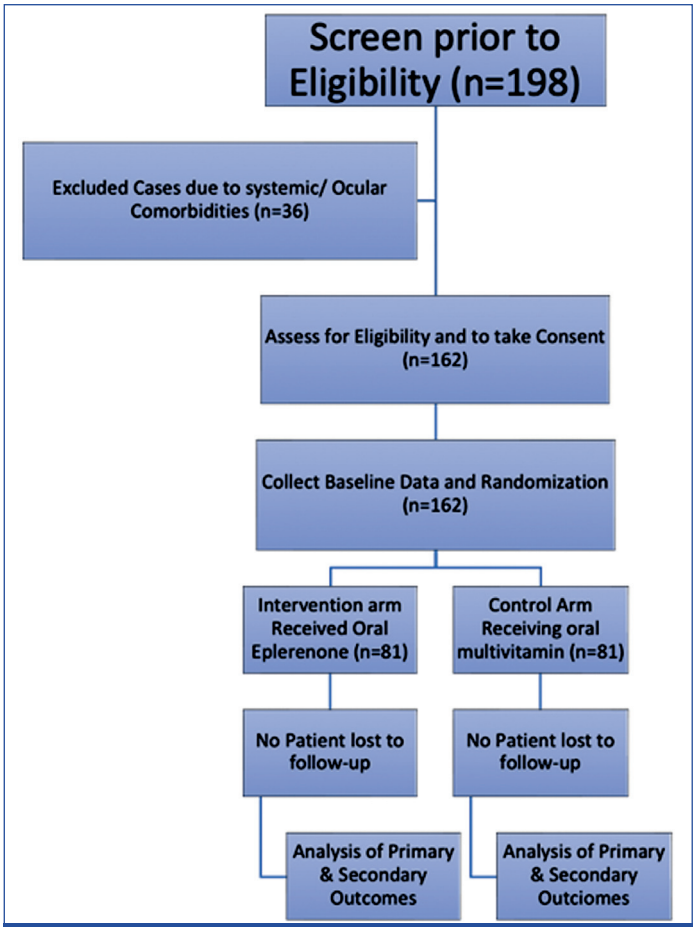
The efficacy of eplerenone in chronic CSCR treatment has already been well documented [3,10-12]. However, its effect on acute CSCR has been rarely studied to date [9-11]. A few studies have analysed the efficacy of oral eplerenone on acute CSCR previously [4,10]. Ours is the first prospective, randomised, placebo-controlled study to investigate the role of oral eplerenone in acute CSCR.

MATERIALS AND METHODS

This was a randomised controlled trial that included a consecutive series of patients with acute CSCR attending the Ophthalmology Outpatient Department (OPD) in a tertiary care hospital from 1st April 2021 to 30th March 2023 who met the inclusion criteria. Institutional Ethical Clearance (IEC) was received prior to initiating the study (IEC approval letter no.- IEC/2021/04). This study protocol followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual patients included in the study.

Based on the CSCR cases in the OPD of the previous year, a minimum sample size of 150 was required. Initially, 198 patients were screened for this study. However, finally, 162 were included based on the eligibility criteria [Table/Fig-1].

The subjects attaining 18 years of age with a clinical diagnosis of acute CSCR for the first occurrence were included in the study. Here, acute CSCR is defined as the presence of subretinal fluid on



[Table/Fig-1]: CONSORT flow diagram depicting the study design over the period of the study duration.

Spectral Domain-OCT (SD-OCT) and duration of visual symptoms for less than 12 weeks [7]. Patients were excluded from the study if there were the presence of features of chronic CSCR or recurrent CSCR (patients with a history of at least one previous episode CSCR attack), presence of Choroidal Neovascular Membrane (CNVM) identified by Fundus Fluorescein Angiography (FFA) and/or SD-OCT, any history of treatment for vitreoretinal disease, patients under treatment with steroids in any form, history of other chorioretinal disorders that would influence the results of the current study (e.g., pathological myopia, diabetic retinopathy, choroiditis, age-related macular degeneration, etc.,), and the presence of any other systemic disorder for which eplerenone was used or contraindicated. Patients who fulfilled the inclusion criteria were assigned to either the treatment group named Group-A, treated with Oral Eplerenone, or Group-B, which was the placebo group. A computer-generated table was used to randomise the cases into two groups.

The previous study had mentioned optimal dosages of Oral Eplenerone [12], but the dosage regimen considered for patients of Group-A was inspired by the VICI trial dosing schedule [13]. Group-A patients were treated with tab. eplerenone (25 mg/day), a single tablet daily for one week, followed by 50 mg/day as a single tablet daily afterward until complete resolution of SRF or until the completion of three months, whichever came earlier. A known complication of hyperkalemia is associated with the use of eplerenone [10]. Therefore, after initiating the treatment, we regularly checked the serum potassium levels in both groups. Serum potassium levels were measured at the initiation of the treatment and then after every month until the conclusion of the study. In case of any episode of drug intolerance, the treatment was decided to be discontinued.

In Group-B, patients were on oral medication of tablet multivitamins, a single tablet once daily after dinner. The follow-up study period was three months.

At baseline, for all diagnosed acute CSCR cases, BCVA on standard Snellen's Charts was measured, followed by a complete ophthalmological examination and imaging by fundus photography and SD-OCT. Patients included in the study were followed-up every month with BCVA, slit lamp bio-microscopy, and SD-OCT examinations.

Pre-treatment and post-treatment visual acuity were measured with a Snellen's chart. For statistical analysis, visual acuity measurements were converted to logMAR values using appropriate formulae [14,15]. At baseline and monthly follow-up visits, the SD-OCT radial macular scan protocol was performed every time. SD-OCT evaluation included CMT analysis and the presence of Sub Retinal Fluid (SRF) using macular thickness maps. We included the machine-generated CMT results for all the calculations to avoid errors related to measurements performed manually.

Comparisons of BCVA, CMT, and serum potassium levels between the treatment and control groups were considered as the main outcomes. Safety analyses were recorded at each visit. The trial was made double-blinded so that the patients were supplied with nearly similar-looking tablets from the hospital's dispensary for both groups, and at the same time, the OCT images of two arms were kept masked to the clinicians while grading the results.

Any patient lost to follow-up in the middle of the study has been excluded from the final calculations. Patients where SD-OCT scan has shown erroneous results due to segmentation error were also not taken into account.

Safety analysis: Safety was assessed through the collection and summary of ocular and non-ocular Adverse Events (AEs), Systemic Adverse Events (SAEs), and ocular assessments as detailed in the patient's medical record.

STATISTICAL ANALYSIS

The SPSS Statistics version 20 software (IBM Corp., Armonk, NY, USA) was used for performing necessary statistical calculations. All quantitative variables were denoted as means±standard deviations. Counts and percentages were used to express categorical variables. Categorical variables were analysed using the Chi-square test, while the t-test was used for quantitative variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

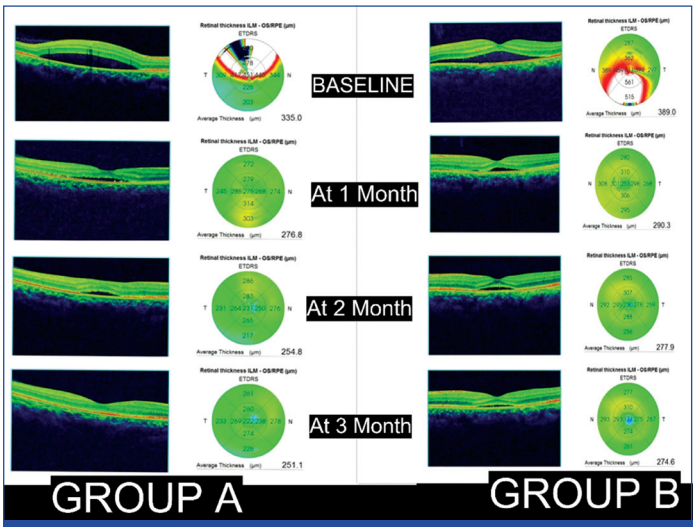
This study included 162 eyes of 162 patients who presented with acute CSCR and underwent a complete evaluation. All the patients were randomly divided into two groups, Group-A and Group-B as mentioned earlier. Both groups were similar in terms of age, gender, laterality, and other baseline parameters. The demographic distribution of the study population and other parameters at baseline is given in [Table/Fig-2].

In Group-A and Group-B, the baseline CMT was 580±126.02 µm and 579±107.97 µm, respectively. After the 1st month in Group-A,

Variables		Group-A (N=81)	Group-B (N=81)	p-value
Age (years)		35.33±9.42	34.26±10.57	0.312*
Sex (M:F)		68:13	70:11	0.516#
Laterality (RE:LE)		42:39	50:31	0.632#
BCVA at presentation (Lines in Snellen's chart)	6/6-6/12	44	40	
	6/18-6/60	18	28	
	<6/60	19	13	
CMT at baseline (µm)		580.43±126.02	578.7±107.97	0.23*
Serum Potassium at baseline (mg/dL)		3.51±0.57	3.47±0.57	0.91*

[Table/Fig-2]: Table showing age, sex, and laterality distribution of the study population along with BCVA, CMT, and serum potassium at baseline comparing both groups.
Chi-square test-*; Student t-test- #

a change of 279±56.41 μm in CMT was noticed compared to 207±68.88 μm in Group-B (p<0.01). At the end of the 3rd month, Group-A patients experienced a total change of 361±33.56 μm compared to 278±46.27 μm in Group-B (p<0.01) [Table/Fig-3].



[Table/Fig-3]: Figure depicts monthly comparative SD-OCT images of macular morphology and central macular thickness in between two representatives of Group-A and Group-B.

Regarding BCVA, there was an average improvement of 3.45±1.08 LogMAR lines in Group-A compared to 2.72±0.93 lines in Group-B at the end of the first month. This improved to 5.12±1.17 LogMAR lines and 3.83±1.04 lines in Group-A and Group-B, respectively, at the end of the second month. Finally, at the end of three months, the improvement was 6.05±1.45 and 4.21±1.23 LogMAR lines in Group-A and Group-B (p=0.002) [Table/Fig-4].

Follow-up	CMT improvement (μm)		p-value	BCVA improvement lines in Log Mar		p-value
	Group-A	Group-B		Group-A	Group-B	
First month	279±56.41	207±68.88	0.034*	3.45±1.08	2.72±0.93	0.07*
Second month	328±46.37	240±61.23	0.027*	5.12±1.17	3.83±1.04	**0.009***
Third month	361±33.56	278±46.27	0.031*	6.05±1.45	4.21±1.23	**0.002***

[Table/Fig-4]: Table showing the monthly comparison of CMT resolution, cure rate, and BCVA improvement along with their statistical supremacy between both the groups.
Student t-test-*

The cure rate and improvement of BCVA have been given in [Table/Fig-5]. The serum potassium level at the conclusion of three months of oral eplerenone therapy in Group-A was increased by 0.61±0.27 mEq/L, while there was minimal change in serum potassium in Group-B (0.1±0.21 mEq/L) during the study period [Table/Fig-5]. There were no AEs that occurred as a result of eplerenone treatment.

DISCUSSION

In the study, a significantly better outcome was observed in the treatment group compared to the observation group. Both anatomical and functional parameters were evaluated for intergroup analysis, providing statistically significant results.

Chatziralli I et al., conducted a meta-analysis of studies published until 2017 regarding oral eplerenone's role in treating CSCR [11]. Summarising the results of 15 studies, they concluded that oral eplerenone in the dose of 25-50 mg/day is effective and well-tolerated for the treatment of chronic CSCR, which aligns with the results of the current study [11]. They also concluded that there was no significant difference between the two dosages [11].

Acute CSCR is usually a self-limiting disorder [9,16]. Patients, even without any treatment, often undergo complete resolution of symptoms in three months or less [9,16]. So, close observation is generally considered the first line of therapy [9]. Nevertheless, a few patients who do not achieve spontaneous recovery can progress to chronic disease, with irreversible visual deterioration and persistent anatomical alterations [9].

Variables	Group-A (N=81)	Group-B (N=81)	p-value
Complete SRF resolution at end of 1st month	45/81 (55.5%)	18/81 (22.2%)	**0.004***
Complete SRF resolution at end of 2nd month	72/81 (88.9%)	53/81 (65.4%)	**0.009***
Complete SRF resolution at end of 3rd month	78/81 (96.3%)	67/81 (82.7%)	**0.03***
Improvement in visual acuity to 6/6 at end of 1st month	58/81	40/81	**0.008***
Improvement in visual acuity to 6/6 at end of 2nd Month	72/81	54/81	**0.009***
Improvement in visual acuity to 6/6 at end of 3rd month	78/81	67/81	**0.03***
Change in serum potassium (mg/dL) at end of 3rd month	0.61±0.27	0.1±0.21	**0.03#**

[Table/Fig-5]: Table showing the number of patients achieving complete SRF resolution and improvement of BCVA to 6/6 in Snellen chart at months 1, 2, and 3 in between two groups and changes in serum potassium at month three in both the groups.
Chi-square test-*; Student t-test- #

Zucchiatti I et al., compared oral eplerenone versus observation in the treatment of acute CSCR in 15 patients [9]. While the treatment group experienced significantly improved BCVA at the 1st month (p = 0.018) and over three months of follow-up (p = 0.011), the observation group could not achieve the same. In the treatment group, SRF and CMT were significantly reduced at the one-month follow-up (p=0.014, p=0.028, respectively) and the three-month follow-up (p <0.001 for both analyses), while in the observation group, the changes were not statistically significant [9]. They concluded that patients with acute CSCR treated with eplerenone experienced better resolution compared to the observation group [9]. In this study, a significantly better outcome was achieved in both groups, but the treatment group achieved a higher cure rate with faster recovery compared to the observation group.

Venkatesh R et al., conducted a prospective randomised study to evaluate the role of oral eplerenone in 58 eyes with acute CSCR [10]. Patients were divided by alternate random sampling into treatment (Table Eplerenone 50 mg/day for a minimum of 1 month) and observation groups, with each group having 29 eyes [10]. BCVA improvement to 6/6 was seen in 92%, 100%, and 100% of cases in the treatment group and 74%, 86%, and 100% in the control group at each visit, respectively, up to three months [10]. Complete SRF resolution in the treatment group was noted in 45%, 55%, and 62% of cases at each respective monthly visit [10]. In the observation group, complete SRF resolution was noted in 10%, 21%, and 31% at 1-, 2-, and 3-month visits, respectively [10]. The p-values between the two groups were statistically significant at all visits [10]. SRF height reduction was significant in both treatment (p <0.001) and control groups (p <0.001) [10]. They concluded that oral eplerenone achieves faster SRF resolution and vision improvement in acute CSCR [10].

Though there was a rise in serum potassium levels, it was well tolerated by patients, and there were no significant adverse effects. Zucchiatti I et al., in their study also did not find any treatment-related side-effects [9]. The same was observed in the study by Venkatesh R et al., [10]. Although none of these articles mentioned any objective serum potassium value in their results.

The advantages of our study were that it was a prospective randomised placebo-controlled study with one of the largest sample sizes compared to other studies.

Limitation(s)

The main limitation of the present study was the short follow-up. Therefore, any data regarding recurrence in long-term follow-up was not recorded for analysis.

CONCLUSION(S)

This study showed that patients affected by acute CSCR and treated with Eplerenone achieved higher and faster resolution of the disease compared to those receiving placebo therapy. Oral eplerenone significantly decreased CMT and improved BCVA in comparison to the placebo group in patients with acute CSCR. Results of this study also indicate that patients undergoing Eplerenone therapy show protection from progressing towards chronic CSCR with permanent RPE changes. Although this study has some limitations, the results of this study showed that eplerenone is an effective non-invasive treatment option for acute CSCR. However, it caused a significant increase in serum potassium levels, and hence close monitoring may be required while prescribing eplerenone to patients with high levels of serum potassium. We believe our effort will encourage future researchers to explore the use of eplerenone in acute CSCR in a more specific way. In conclusion, eplerenone may represent an attractive new first-line treatment option for acute CSCR.

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