Efficacy of Drug Eplerenone in the Management of Chronic Central Serous Chorioretinopathy

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ABSTRACT

BACKGROUND

Central serous chorioretinopathy (CSCR) is the fourth most common retinopathy after age-related macular degeneration, diabetic retinopathy and branch retinal vein occlusion. Chronic Central Serous Chorioretinopathy is defined as persistence of sub-retinal fluid on Ocular Coherence Tomography beyond 3 months of onset of the disease. In the current study, we evaluated the efficacy of eplerenone in patients of chronic serous chorioretinopathy (CSCR).

METHODS

It is a randomized double blind study of sixty-eight eyes of sixty patients who were randomized into two groups. Thirty-five eyes of thirty patients in the treatment group (Group A), received 50 mg eplerenone daily for 3 months and thirty-three eyes of thirty patients in the control group (Group B) received one capsule of placebo drug (glucose powder) each day for the same duration. Visual acuity (VA), maximum height of sub-retinal fluid (SRF) and contrast sensitivity (CS) were studied at baseline and monthly thereafter for 6 months after initiation of therapy.

RESULTS

Better improvement of VA, reduction of SRF and improvement of CS were observed in the treatment group as compared to placebo. t-Test showed that there was significant difference in mean CS of the two groups at 6 months (p= 0.0459) and it also showed that there was significant difference in mean SRF of the two groups at the end of 6 months (p= 0.0491).

CONCLUSIONS

Eplerenone could be beneficial as an alternate mode of therapy in the treatment of chronic CSCR.

KEYWORDS

Chronic Central Serous Chorioretinopathy, Eplerenone, Sub Retinal Fluid, Contrast Sensitivity

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BACKGROUND

Chronic Central Serous Chorioretinopathy (CSCR) is defined as persistence of sub-retinal fluid on Ocular Coherence Tomography beyond 3 months of onset of the disease. It is the fourth most common retinopathy after age-related macular degeneration, diabetic retinopathy and branch retinal vein occlusion.[1] It is characterized by serous retinal detachment and/or retinal pigment epithelial (RPE) detachment, changes most often confined to the macula, and associated with leakage of fluid through the RPE into the subretinal space. It typically occurs in males in their 20s to 50s who exhibit acute or sub-acute central vision loss or distortion along with other common complaints like micropsia, metamorphopsia, hyperopic or myopic shift, reduced contrast sensitivity and color saturation.[2] CSCR usually resolves spontaneously within 2 to 3 months, so newly presenting cases are kept under observation.[3] Recurrence occurs in about 31% patients with CSCR.[4] In the current study we evaluated the efficacy of drug eplerenone in patients of chronic CSCR. Eplerenone is an antagonist of the mineralocorticoid receptor, having 10- to 20- fold lower affinity for the mineralocorticoid receptor relative to spironolactone.

METHODS

The current study was a randomized controlled double blind study conducted from January 2016 to July 2017 in the retina department of a tertiary eye care centre. It comprised of patients attending the out-patient department diagnosed as chronic CSCR. The study was approved by the Institutional ethics committee for human research. Patients were randomized according to a computer generated randomization schedule into either group (Group A: eplerenone, Group B: placebo). Eplerenone drugs and placebo (glucose powder) were dispensed in identical looking empty capsules in sequentially numbered opaque sealed envelopes. The study group was given 50 mg of eplerenone once daily for 3 months and the control group was given one capsule of placebo drug each day for the same time period. Patients of acute CSCR, patients presenting with intra-retinal or sub-retinal oedema secondary to other causes such as diabetic retinopathy and retinal venous occlusive disorders or any other retinal disease and patients with vitreous haemorrhage or any other causes of media opacity were excluded from our study.

The following baseline characteristics of each group were studied: Age (in years), gender, laterality of the eye, history of previous exposure to steroids, duration of symptoms, visual acuity (Snellen's visual acuity chart), contrast sensitivity(Pelli-Robson chart) and maximum height of sub-retinal fluid (Spectral Domain Optical Coherence Tomography, Heidelberg engineering). The visual acuity, contrast sensitivity (CS) and maximum height of sub-retinal fluid (SRF) were measured at the end of each month after initiation of therapy up to a period of 6 months. Statistical analysis was performed with help of Epi Info (TM) 3.5.3 which is a trademark of the Centers for Disease Control and Prevention (CDC).Using this software, basic cross tabulation and frequency distributions were prepared. x^2 test was used to test the association between different study variables under study. Corrected x^2 test was used in case of any one of cell frequency was found less than 5 in the bivariate frequency distribution. Test of proportion (Z-test) was used to test the significant difference between two proportions. t-test was used to test the significant difference between means. Also, One Way Analysis of variance (ANOVA) followed by post-hoc Tukey's Test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values. $p<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Sixty-eight eyes of sixty patients were included in the study. Thirty-five eyes of thirty patients in the eplerenone group (Gr. A) and thirty-three eyes of thirty patients in the placebo group (Gr. B). There was no significant differences in age distribution, gender distribution, laterality of eyes, duration of symptoms and history of steroid exposure (p=0.12–0.99). The mean age of patients in this study was 34.06 years. Eight out of sixty patients were females (13.33%) and eight had bilateral CSCR (13.33%). The mean contrast sensitivity at presentation was 0.34±0.30 in group A and 0.37±0.30 in group B (p=0.61). The mean maximum SRF height at presentation was 138.70±64.55μ in group A and 136.15±65.27μ in group B (p=0.85).

Visual Outcomes

Corrected Chi-square (x^2) test showed that there was no significant association between BCVA and patients of the two groups at different time interval. However, test of proportion showed that BCVA improved significantly at different time interval as compared to at-presentation ($p<0.05$). The better improvement was observed in Group A as compared to Group B (Table 1).

Contrast Sensitivity (CS)

The mean CS had increased from 0.34±0.30 at presentation in the eplerenone group to 0.56 ± 0.38 at the end of 3 months of medication but dropped slightly to 0.56 ± 0.37 at 3 months post treatment. The mean CS had also increased from 0.37±0.30 at presentation in the placebo group to 0.44 ± 0.36 at the end of 3 months of medication and further increased to 0.48 ± 0.39 at 3 months post treatment. t-test showed that there was no significant difference in mean CS of the two groups except at 5 months (p=0.0459). At 5 months the mean CS of Group B was significantly lower than that of Group A ($p<0.05$). However, the mean CS of Group B was lower than that of Group A after 2 months and onwards. Corrected Chi-square (x^2) test showed that there

was no significant association between contrast sensitivity and patients of the two groups at different time interval. However, test of proportion showed that contrast sensitivity improved significantly at different time interval as compared to at presentation ($p<0.05$). The better improvement was observed in Group A as compared to Group B (Table 2)**.**

Maximum Sub-Retinal Fluid Height (SRF):

The mean SRF had decreased from 138.70±64.55 µ at presentation in the eplerenone group to 74.51±80.29 µ at the end of 3 months of medication but slightly increased to 75.94±77.64 µ at 3 months post treatment. The mean SRF had also decreased from 136.15±65.27 µ at presentation in the placebo group to 113.69±72.90 µ at the end of 3 months of medication and further decreased to 107.33±78.57 µ at 3 months post treatment. t-test showed that there was significant difference in mean SRF of the two groups except at 1 month. 2 month onwards the mean SRF of Group A was significantly lower than that of Group B ($p=0.041$, $p=0.0134$, $p=0.0173$, $p= 0.0178$ and $p=0.0491$ at 2,3,4,5 and 6 months after initiation of therapy. Corrected Chi-square (x^2) test showed that there was significant association between SRF height of the patients of the two groups at 2 months onwards ($p<0.05$). Also, test of proportion showed that SRF height reduced significantly at different time interval as compared to at presentation ($p<0.05$). The better reduction was observed in Group A as compared to Group B. (Table 3)

BCVA	At Presentation		At 1 Month		At 3 Month		At 6 Month	
	Gr-A	Gr-B	Gr-A	Gr-B	Gr-A	Gr-B	Gr-A	Gr-B
6/6 - 6/12	8	8	12	8	23	17	23	17
Row%	50.0	50.0	60.0	40.0	57.5	42.5	57.5	42.5
Col%	22.9	24.2	34.3	24.2	65.7	51.5	65.7	51.5
6/18 - 6/36	11	13	11	12	6	5	7	6
Row%	45.8	54.2	47.8	52.2	54.5	45.5	53.8	46.2
Col%	31.4	39.4	31.4	36.4	17.1	15.2	20.0	18.2
6/60 - 3/60	14	9	10	10	5	8	4	6
Row%	60.9	39.1	50.0	50.0	38.5	61.5	40.0	60.0
Col%	40.0	27.3	28.6	30.3	14.3	24.2	11.4	18.2
2/60 and Worse	2	3	2	3	1	3	1	4
Row%	40.0	60.0	40.0	60.0	25.0	75.0	20.0	80.0
Col%	5.7	9.1	5.7	9.1	2.9	9.1	2.9	12.1
Total	35	33	35	33	35	33	35	33
Row%	51.5	48.5	51.5	48.5	51.5	48.5	51.5	48.5
Col%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Chi-square	1.39		0.98		2.62		3.12	
(x^2)	0.70		0.80		0.45		0.37	

Table 1. Distribution of Best Corrected Visual Acuity (BCVA) of Patients of the Two Groups

CS at Different Time Interval	Group-A (n=50) (Mean ± S.D.)	Group-B (n=50) (Mean ± S.D.)	Test Statistic (t98)	p
At presentation				
Median	0.30	0.45		
Range	0.00 - 0.90	0.00 - 0.75		
At 1 month				
Mean ± S.D.	0.39±0.33	0.35±0.30	0.63	0.53
Median	0.30	0.30		
Range	0.00 - 1.20	0.00 - 0.90		
At 2 month				
Mean ± S.D.	0.57±0.41	0.42±0.34	2.01	0.091
Median	0.60	0.45		
Range	0.00 - 1.50	0.00 - 0.90		
At 3 month				
Mean ± S.D.	0.56±0.38	0.44±0.36	1.62	0.11
Median	0.75	0.60		
Range	0.00 - 1.35	0.00 - 0.90		
At 4 month				
Mean ± S.D.	0.58±0.38	0.46±0.37	1.59	0.12
Median	0.75	0.60		
Range	0.00 - 1.35	0.00 - 1.05		
At 5 month				
Mean ± S.D.	0.58±0.38	0.47±0.38	2.04	0.0459
Median	0.75	0.60		
Range	0.00 - 1.35	0.00 - 1.20		
At 6 month				
Mean ± S.D.	0.56±0.37	0.48±0.39	1.05	0.29
Median	0.75	0.60		
Range	0.00 - 1.20	0.00 - 1.20		

Table 2. Comparison of Contrast Sensitivity (CS) at Different Time and Patients of the Two Groups

Time	Group-A (n=50) (Mean ± S.D.)	Group-B (n=50) (Mean ± S.D.)	Test Statistic (t98)	p-Value
At Presentation				
Median	123.50	121.00		
Range	21 - 296	21 - 296		
At 1 Month				
Mean ± S.D.	114.75±72.08	131.90±65.70	1.24	0.22
Median	100	119		
Range	0 - 297	21 - 297		
At 2 Month				
Mean ± S.D.	91.11±78.07	122.24±70.22	2.09	0.041
Median	83	100		
Range	0 - 299	13 - 299		
At 3 Month				
Mean ± S.D.	74.51±80.29	113.69±72.90	2.55	0.0134
Median	54	97		
Range	0 - 293	0 - 293		
At 4 Month				
Mean ± S.D.	72.86±79.69	110.96±75.90	2.45	0.0173
Median	53	94		
Range	0 - 299	0 - 299		
At 5 Month				
Mean ± S.D.	72.86±79.69	110.96±75.90	2.44	0.0178
Median	53	94		
Range	0 - 299	0 - 299		
At 6 Month				
Mean ± S.D.	75.94±77.64	107.33±78.57	2.01	0.0491
Median	57.5	97		
Range	0 - 303	0 – 303		

Table 3. Comparison of SRF at Different Time and Patients of the Two Groups

DISCUSSION

Most patients who present with CSCR are between the ages of 28 to 68 years with an average age of 43 years.[5] CSCR tends to affect males (9.9/100,000) about six times more than females (1.7/100,000). Although exact mechanisms behind CSCR have not been elucidated, many associations have been found. Garg and colleagues found that patients with acute CSCR have higher levels of endogenous cortisol compared to age-matched. Exogenous steroid, Methylenedioxymethamphetamine (MDMA), Sildenafil, Sorafenib and Vemrafenib have also been associated with development of CSCR.[6] CSCR's association with having a type A personality seems logical given known increased glucocorticoid release with stress.[7] Various prospective studies revealed that H.pylori infection was present in 53% and 69% of patients with CSCR. Other common risk factors include pregnancy, antibiotic use, alcohol use and untreated hypertension.[8] Spironolactone, an anti-corticosteroid has been shown to decrease sub-retinal fluid, decrease central retinal thickness, and increase BCVA in patients with chronic CSCR. Finasteride, a 5a-reductase inhibitor with anti-androgenic properties, was shown to improve central

macular thickness (CMT) and sub-retinal volume in a study of five patients but these findings reversed when the drug was discontinued.[9] The use of anti-vascular endothelial growth factor (VEGF) agents are based on the idea that VEGF levels may be elevated due to the choroidal pathology. However, studies have shown that VEGF levels are similar between CSCR patients and control patients.[10] Sub-threshold micro pulse laser (SML), also known as "high density, low-intensity" laser, uses sub-threshold energy that selectively targets RPE cells without inducing chorio-retinal damage. Unlike conventional laser, SML can be safely applied to the fovea. In the current study, we compared the efficacy of eplerenone, a steroidal anti-mineralocorticoid of the spironolactone group in patients of CSCR. Eplerenone have 10- to 20- fold lower affinity for the mineralocorticoid receptor relative to spironolactone,[11] and is less potent in vivo as an anti-mineralocorticoid.[12] However, in contrast to spironolactone, eplerenone has little affinity for the androgen, progesterone, and glucocorticoid receptors. It also has more consistently observed non-genomic anti-mineralocorticoid effects relative to spironolactone. The manufacturer of eplerenone also contraindicates concomitant treatment with ketoconazole, itraconazole or other potassium sparing diuretics. Eplerenone is contraindicated in patients with hyperkalaemia, severe renal impairment or severe hepatic impairment. In our study better improvement of visual acuity, reduction of SRF and improvement of CS was observed in the eplerenone group as compared to placebo. The mean CS had increased from 0.34±0.30 at presentation in the eplerenone group to 0.56±0.37 at the end of our study period whereas the mean CS had only increased from 0.37±0.30 at presentation in the placebo group to 0.48±0.39 during the same study period. t-test showed that there was no significant difference in mean CS of the two groups except at 5 months ($p=0.0459$). Test of proportion showed that contrast sensitivity improved significantly at different time interval as compared to presentation ($p<0.05$). The better improvement was observed in Group A as compared to Group B. The mean SRF had decreased from 138.70±64.55 µ at presentation in the eplerenone group to 75.94±77.64 µ at the end of the study period whereas the mean SRF had only decreased from 136.15±65.27 µ at presentation in the placebo group to 107.33±78.57 µ during the same period. t-test showed that there was significant difference in mean SRF of the two groups at the end of 6 months. 2 month onwards the mean SRF of Group A was significantly lower than that of Group B ($p=0.041$, $p=0.0134$, $p=0.0173$, $p= 0.0178$ and $p=0.0491$ at 2,3,4,5 and 6 months after initiation of therapy). Test of proportion also showed that SRF height reduced significantly at different time interval as compared to at presentation ($p<0.05$). The better reduction was observed in Group A as compared to Group B. Rahimy E et al.[13] in his study showed similar improvements in anatomical and functional status following eplerenone therapy. But there was no mention about contrast sensitivity in his study. We in our study have demonstrated the changes in contrast sensitivity as a result of treatment with eplerenone in chronic CSCR patients. Similar results were also observed by Schwartz R et al.[14] but they concluded that eplerenone was not superior to placebo in these patients as the results were not statistically significant. In this study no patient was lost to follow up. One patient suffered from elevated blood glucose level at the end of three months of intake of medication although the blood glucose level returned to normal levels after stopping therapy.

Limitations

Other mineralocorticoid receptor antagonists have not been compared to eplerenone in this trial. Also the effect of eplerenone in preventing recurrence of the disease and also its long term safety and efficacy could not be evaluated as longer follow up period was required for the same.

CONCLUSIONS

Given the high incidence of bilateral chronic CSCR, oral eplerenone may be beneficial at treatment initiation as it leads to reduction in sub-retinal fluid and improvement of visual acuity and contrast sensitivity in such eyes. Other treatment modalities such as focal laser photocoagulation or PDT may be tried when oral eplerenone fails. Eplerenone targets the entire retina versus specific areas as in cases of focal laser and PDT. Moreover, PDT is invasive in nature and costly. Additionally, laser photocoagulation treatment was not shown to reduce the incidence of recurrent or chronic CSCR and is more effective in acute CSCR. Oral eplerenone is also less invasive and cheaper than laser treatment and anti-VEGF injections. Despite the limitations stated earlier results of this study indicate that eplerenone could be beneficial in the treatment of unresolved CSCR.

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