ORIGINAL RESEARCH PAPER

Ophthalmology

EVALUATION OF THE EFFECTS OF CHLOROQUINE PHOSPHATE EYE DROPS IN PATIENTS WITH DRY EYE SYNDROME

KEY WORDS:

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ABSTRACT

OBJECTIVES: To evaluate the efficacy and safety of 0.03% chloroquine phosphate eye drops in comparison with artificial tears for the treatment of dry eye syndrome.

METHODS: A prospective, randomized, case control study was conducted on 240 eyes of 120 patients which were assigned into 2 groups-

GROUP: 1 Carboxymethyl Cellulose (CMC), 60 patients, Dose: 0.5%, 2-4 times / day

Group: 2 Chloroquine phosphate (CHQ), 60 patients, Dose: 0.03%, twice a day

Main outcome measures included efficacy aspects viz. Lissamine Green Stain Score (LGSS), Fluorescine Stain Score (FLSS), Schirmer test, and Ocular Surface Disease Index (OSDI) .

RESULTS: The most significant improvements with CHQ treatment were in LGSS from baseline (2.79±0.12) to (0.22±0.04) after treatment ($p < 0.001$) with the net change -2.57 (95% CI of -2.83 to -2.32). CHQ treated group also reflected significant reduction in FLSS at final visit (0.47±0.065) as compared to baseline (3.21±0.12) with a net change of -2.74 (95% CI of -3.007 to -2.451). Significant decrease in OSDI scores indicated a decrease in the effect of ocular symptoms on patients' daily lives.

CONCLUSIONS: CHQ eye drops were found to be more effective, safe and well tolerated than artificial tears in patients with dry eye syndrome.

INTRODUCTION

Dry eye syndrome (DES) is "a disorder of the tear film attributable to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort." Recent studies have revealed that inflammatory component as the main causative factor of the disorder. Cytokine and receptor mediated inflammatory cascade disintegrates the tear film layer by affecting the lacrimal gland acini and ducts and disturbs ocular surface homeostasis.[2] Apoptosis has also been implicated in the pathogenesis of dry eyes.[3]

Current therapies for the management of dry eye include drugs for tear supplementation, retention, and stimulation; anti- inflammatory agents; and environmental strategies.[4] Palliative therapies like tear substitutes are currently the most common choice of treatment but have failed to yield high success rates because they give only symptomatic improvement but do not treat underlying cause of disease. The major anti-inflammatory agents currently in use include topical corticosteroids and immunomodulatory agents.[5,6]

Topical chloroquine may provide a unique opportunity to move beyond treatments that only alleviate the symptoms of dry eye disease to therapies that effectively target the inflammatory processes contributing to disease pathogenesis.[14] the present study was carried out to compare the efficacy, safety and patient tolerability of topical chloroquine phosphate (0.03%) with artificial tear.

METHODS

2.1. Study Design

A prospective, randomized, open label, two way, split plot design study was conducted on 240 eyes of 120 patients at Department of ophthalmology, Govt. Medical College & Group of Hospitals, Kota, in compliance with the institutional review board regulations (Human Research Ethics Committee) and informed consent regulations. Before initiation of study, written informed consent was taken from subjects.

2.2. Inclusion and exclusion criteria

Inclusion criteria (age between 18-70 year)-

1. One or more moderate dry eye–related symptoms, including itching, burning, blurred vision, foreign body sensation, dryness, photophobia, and soreness or pain i.e. a Ocular Surface Disease Index [OSDI] score between 13 and 100, best visual acuity of 6/18 or better in each eye. Both eyes were treated and included in all analysis (see statistical analysis).
2. Tear Break up time of less than 10 seconds
3. Schirmer test-1 score less than 10 mm/5min.
4. Rose Bengal score more than 3.5.

Exclusion Criteria:-

1. Patients with allergies like vernal keratoconjunctivitis, atopic conjunctivitis, seasonal allergic conjunctivitis, contact allergy.
2. Chronic bacterial or viral ocular infections.
3. Patient with corneal degeneration and dystrophy .
4. Patient with any ocular disorder including ocular injury, infection, Non dry eye ocular inflammation
5. Trauma, surgery within period of six month and any uncontrolled systemic diseases or significant illness.
6. Contact lens wear, subject that require surgical correction of dry eye, known case of hypersensitivity to chloroquine chronic alcoholic pregnant women, willing to get pregnant, nursing women.

2.4. Sequence and duration of all study periods

Patients were randomly assigned into 2 different treatment groups-

Group: 1 Carboxymethyl Cellulose (CMC) (0.5 %, 2-4 t / day)

Group: 2 Chloroquine phosphate (0.03%, 2 t/ day).

All the subjects received treatment for 21 days during which they were evaluated on visit 1 (day 0), visit 2 (day 7), visit 3 (day 14) and visit 4 (day 21). Seven days after termination of the treatment subjects were assessed on visit 5 (day 28).

2.5. Outcome Measures

Parameters under investigation:

A) Efficacy parameters
1. Objective end points: LGSS, FLSS, Schirmer's test
2. Subjective end points osdi

B) Safety Parameters

Treatment safety assessments included vital signs, slit-lamp examination, best corrected visual acuity (BCVA), macular function, intraocular pressure (IOP), color vision, dilated fundus examination, and collection of adverse events (Aes)

Table 1: Changes of efficacy measures with different treatment groups

Efficacy Measures	Baseline value(BL) (Day 0)	After treatment				P Value
		V1 (Day 00 7)	V2 (Day 77714)	V3 (Day 21)	V4 (Day 28)	
Lissamine Green Stain Score (LGSS)						
CMC	1.98±0.13	1.71±0.31	1.24±0.2	1.11±0.11*	1.02±0.12*	P<0.05
CHQ	2.79 ±0.12	1.74 ±0.10*	0.72±0.07*	0.22 ± 0.04*	0.14 ±0.03*	P<0.001
Fluorescein Stain Score (FLSS)						
CMC	2.91±0.14	2.44 ±0.13	1.92±0.12	1.52±0.01*	1.36±0.09*	P<0.05
CHQ	3.21±0.12	1.99±0.10*	1.02±0.09*	0.47±0.07*	0.40±0.06*	P<0.001
Schirmer test						
CMC	12.78±0.3	13.24±0.3	13.77±0.2	13.92±0.2*	13.65±0.26	P<0.05
CHQ	12.43±0.4	13.39±0.4	14.14±0.3*	14.95±0.3*	14.98±0.38*	P<0.001
Ocular Surface Disease Index (OSDI)						
CMC	54.53±1.3	45.26±1.1*	37.92±1.2*	32.29±1.1*	33.52±1.8*	P<0.05
CHQ	61.42±2.1	43.1±1.9*	28.36±1.8*	18.71±1.5*	16.67±1.4*	P<0.05

All data are presented as mean±SEM. Anova followed by Tukey's test. Asterisk indicates significant difference from baseline ($p < 0.05$)

Table 2:Treatment Related Adverse Events

Adverse Event	CMC (n=60	CHQ (n=85)	Total Events (n=170)
Conjunctival hyperemia	1 (0.4%)	1 (0.4%)	2 (1.17%)
Burning eye	1 (0.4%)	2 (0.8%)	3 (1.2%)
Pain in the eye	0	1 (0.4%)	1 (0.4%)
Visual disturbance	2 (2.35%)	0	2 (1.17%)
Total patients	2 (2.35%)	2 (2.35%)	4 (2.35 %)

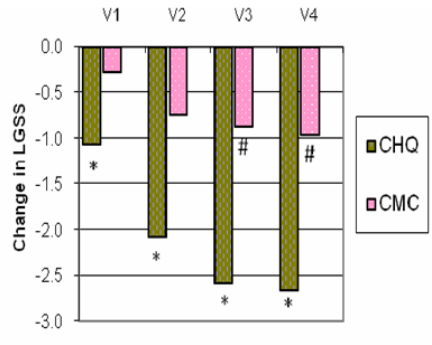


Figure 1. Change from baseline in Lissamine Green Stain Score

* indicates statistical significance ($p<0.001$), # indicates statistical significance ($p<0.05$)

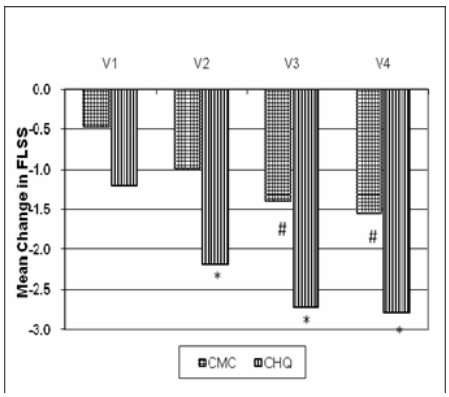
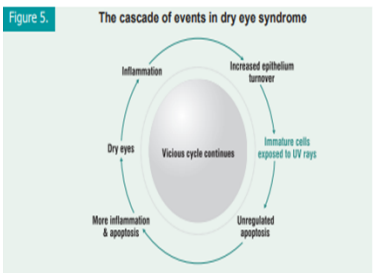


Figure 2. Change from baseline in Fluorescine Stain Score

DISCUSSION



Occurrence of damage to ocular surface, mainly cornea conjunctiva and lacrimal gland secretion are the major signs observed in DES. Conjunctival staining indicates epithelial cell damage and therefore, necessarily damage to the overlying gel-like mucin layer.

Corneal fluorescein staining was improved significantly after CHQ treatment as early as the first week. Decreasing corneal fluorescein staining is due to the suppression of inflammation. Further, CHQ treated group showed significant relief from symptoms for different categories namely ocular symptoms, vision related functions and environmental triggers based on the results of % OSDI score.

The lysosomotropic effects of CHQ are widely believed to be responsible for its anti-inflammatory properties and effectiveness in the treatment of some autoimmune diseases. It is reported that CHQ decreases the production of the pro-inflammatory cytokines IFN- , tumour necrosis factor-alpha (TNF-), and interleukin-6 (IL-6) in Lipopolysacharide (LPS)- or phytohemagglutinin stimulated peripheral blood mononuclear cells[23], and CHQ also known to exert anti-inflammatory effects via non- lysosomotropic mechanisms.[25]

CHQ inhibits metalloproteases liberated by macrophages, neutrophils and the dead or dying cells.

Topical CHQ is reported as protective against UV radiations, particularly UVB and UVA induced erythema in skin.[33] Besides anti-inflammatory properties, CHQ could also have photo-protective effects .

Toxicity and adverse effects of CHQ are well documented in the literature. But they are related to high cumulative

systemic dose. CHQ when given topically at 0.03% dose twice a day for 21 days, as in present study, the total dose reaching local ocular tissue or absorbed systemically is very minute fraction of the toxic cumulative dose. for So there is no question of any local or systemic side effect CHQ.

The safety of CHQ is well established in our study and the benefit-to-risk evaluation is overwhelmingly positive. CHQ, despite its well documented toxicity and adverse effects may have important future uses that are associated with its lysosomotropic and immunomodulatory mechanisms.[33]

Thus, the rapid treatment effect realized by administration of CHQ is highly relevant in the treatment of this disease.

RESULTS

A total of 41 (28.8%) male and 79 (71.2%) female patients were reflecting mean age of 53 ± 10.5 years (22 ~ 77). There were no statistically significant differences in age, gender, and pretreatment tear film and ocular surface parameters between the two groups (Table 1).

3.1. Outcome Measures

1. Efficacy Measures

The efficacy measures were in terms of LGSS, FLSS, Schirmer test and the global assessment scoring system - OSDI.

1. Efficacy Analysis of LGSS

Based on our data, group mean values, as well as the magnitude of the net change in LGSS for any particular cohort were calculated. In addition, relative changes in LGSS were calculated as the percentage change from baseline.

CHQ treated group showed significant reduction in LGSS at all the visits (P<0.05). The group mean scores was found to be (2.79±0.12) at baseline and (0.22±0.04) after treatment (P< 0.001) with the net change -2.57 (95% CI of - 2.83 to -2.32). It is also to be noted that CHQ also showed significant reduction in LGSS even at visit 1 & 2 (P<0.001). CMC treatment showed significant change in mean score only at visit 3 i.e. 1.11±0.11(V3) from 1.98±0.13 (BL) with a net change of -0.87 (95% CI of - 1.21 to -1.55) (P<0.05) (Table 2).

Treatment with CHQ showed substantial changes in terms of significant reduction in LGSS as compared to CMC (fig 1). Analysis of comparison of both the treatments vs. baseline scores on a 94.21% respectively for CHQ and 44.21% for CMC treatments.

3.1.1.2. Efficacy Analysis of FLSS

CHQ treated group reflected significant reduction in FLSS from 3.21±0.13 (BL) to 0.47±0.07 (V3) (p<0.001) significant with the net change-2.74 (95% CI of -3.007 to -2.451). Significant with the net change of reduction was noted at the end of visit 1 (Table 2). CMC treated group indicated significant reduction in FLSS only at visit 3 from 1.52±0.01 as compared to 2.91±0.14 at baseline (P <0.05) with a net change of just -0.39 (95% CI of -1.72 to -1.06) (fig 2). Further, the percentage improvement in CHQ and CMC groups were 51% and 28% respectively.

3. Efficacy Analysis of Schirmer test

Baseline values for schirmer tear strip wetting scores ranged from 12.43 to 12.78 in both the treatment groups. The most consistent improvement was observed in the CHQ treated group, with mean increase in wetting length of (13.39±0.41), (14.14±0.39), (14.95±0.39) and (14.98 ±0.38) mm at week one, two, three and four respectively when compared with the baseline (12.43±0.44) values. These increases approached statistical signifi- cance at week 2 (P<0.05); week 3 (P<0.001) and week 4 (P<0.001) (table 2). The significant improvement from baseline occurred in the CMC group at treatment week 3 only (P<0.05). Further, in support of above findings, a net change of 2.52 (95% CI of 1.37 to 3.67) in mean schirmer value of CHQ treated patients was observed as compared to a net change of 1.14 (95% CI of 0.36 to 1.92) with CMC group. It is to be noted that the % improvement was found higher with CHQ treatment (20%) as compared to CMC treatment (9%).

3.1.1.4. Efficacy Analysis of OSDI

Baseline OSDI scores ranged from 54 to 61 (on a scale from 0 to 100, where 0 indicates no disability and 100 indicate complete disability) in both the treatment groups. CHQ treated group reflected highly significant reduction in OSDI at visit 3 (18.71±1.5) as compared to baseline (61.42 ± 2.11) with a net change of -42.71 (95% CI of -47.4284 to -39.8) (p<0.05) (Table 2). The mean baseline score for CMC treated group change significantly (p<0.05) from 54.53±1.33 (BL) to 32.29±1.16 (V3) with a net change -22.24 (95% CI of -25.69 to -18.79). Both CHQ and CMC treated groups indicated significant reduction in OSDI at every visit when compared with the baseline. Thus, substantial change in OSDI has been achieved with the use of CHQ in terms of net reduction of score. Based upon these findings, we further tried to segregate different categories of problems i.e. ocular symptoms, vision related functions and environmental triggers in patients. Mean OSDI significantly decreased from baseline to final assessment (V3) in all 3 categories of problems indicating robust improvement with CHQ treatment. Percentage improvement in CMC and CHQ treated groups were found 40.8% and 69.5% respectively.

Both the treatments were further evaluated for the % efficacy of each group across the different category of problem. CHQ treatment showed significant improvement in ocular symptoms, vision related functions and environmental triggers as compared to CMC treatment.

CONCLUSION

It can be clearly inferred from the findings that the difference in the two groups with respect to improvement was due to the CHQ treatment suggesting independent favorable effect of it in DES. The findings of this study support the continued investigation of the use of topical CHQ as a safe and effective treatment for DES.

In conclusion, Chloroquine Phosphate eye drops can be a novel therapeutic approach for the restoration of tear formation for DES.

DISCLOSURE:-

The authors have no proprietary or commercial interest in any materials discussed in this article.

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