COMPARISON OF THE EFFICACY OF TOPICAL CYCLOSPORINE WITH FLUROMETHALONE IN TREATMENT OF DRY EYE DISEASE

Nadia Erum, Abdul Majeed Malik*, Amir Yaqub, Zaheer Akhtar***, Ayaz Rasul**

Heavy Industries Taxila (HIT) Hospital, Taxila/ National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, **Armed Forces Institute of Ophthalmology (AFIO)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, ***DMS HQ log Sc, Quetta Pakistan

ABSTRACT

Objective: To compare the efficacy of 0.05% cyclosporine eye drops with 0.1% fluromethalone eye drops on keratoconjunctivitis sicca (dry eye disease).

Study Design: Randomized controlled trial.

Place and Duration of Study: Ophthalmology department of HIT Hospital Taxila, from Oct 2014 to May 2015.

Material and Methods: The patients with keratoconjunctivitis sicca (KCS) were selected from outpatient and divided in two treatment groups. The dry eye disease was defined according to criteria set by International task force for dry eye disease (ITF). The group I was treated with 0.05% cyclosporine drops while group-II was treated with 0.1% fluromethalone eye drops three times a day after informed written consent. The patients were followed up after three months and six months.

Results: At the start of treatment 94 patients were placed in two treatment groups (n=47 in each group) and all the patients with KCS were graded according to severity following rules set by ITF. There were 46 patients in grade III (severe) KCS and 20 patients in grade IV (very severe) KCS. At the end of study only 24 were in grade II (moderate) KCS and 2 in grade III KCS.

Of these only 5 patients in grade II and none in grade III were in treatment group I (cyclosporine). The remaining 19 patients in grade II and 5 patients in grade III KCS belonged to group II (fluromethalone).

Conclusion: Cyclosporine eye drops are better than fluromethalone in treatment of keratoconjunctivitis sicca.

Keywords: Cyclosporine, Dry eye disease, Fluorescein staining, International task force (ITF) guidelines, Keratoconjuctivitis sicca (KCS), Schirmer test, Tear break up time (BUT).

INTRODUCTION

The potential of cyclosporine-A for treating dry eye disease was initially recognized in dogs who developed spontaneous keratoconjunctivitis sicca. The therapeutic efficacy of cyclosporine for human KCS was then documented in several small single center clinical trials[1-5]. The cyclosporine is underutilized drug in Pakistan with no clinical trials in our country. Furthermore there is decreased expression of immune activation markers (i.e. HLA-DR), apoptosis markers (i.e. Fas) and the inflammatory cytokines IL-6 by conjunctival epithelial cells[6].

Cyclosporine is an immune modulator[7-11]. It increases conjunctival goblet cell density by 200%.No cyclosporine was detected in blood of patients treated with cyclosporine eye drops[12-15]. (Ropsol eye drops by Atco).

The topical corticosteroid (Fluromethalone) is effective anti-inflammatory therapy in dry eye disease. Level III evidence is available to support the efficacy of corticosteroid in KCS. But short term and long term therapy is associated with its hazards which sometimes outweigh the treatment[16-18].

The rationale of study was to compare the two treatment modalities to see which one is more effective in our population according to international guidelines of ITF[19,20].

PATIENTS AND METHODS

The randomized controlled trial was carried out at the department of ophthalmology H.I.T Hospital Taxila cantt from October 2014 to May

2015. Patients of both gender were included in the study. All the cases selected for study were under the criteria set and approved by the american academy of ophthalmology and international task force Delphi pane for dry eye disease. Inclusion criteria was tear break up time less than 10 seconds, Schirmer test score of less than 10 mm and fluorescein staining of at least one area out of three pre-selected areas. Patients with significant ocular pathologies like herpes

from the institution ethical committee and informed consent was taken for this study.

All the patients were selected and categorized according to guidelines set by ITF utilizing tear breakup time (BUT), Schirmer test I, and fluorescein staining of conjunctiva and cornea as standard criteria[1,2,10,12,16].

The group I was treated with topical 0.05% cyclosporine eye drops and standard topical lubricant and group II was treated with topical
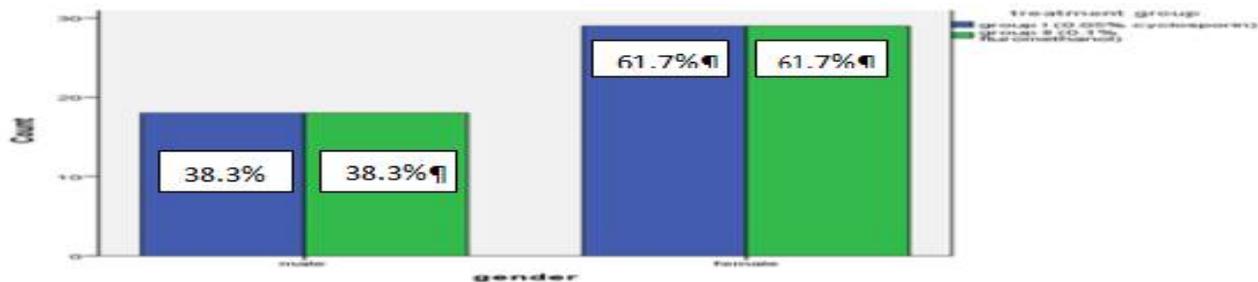

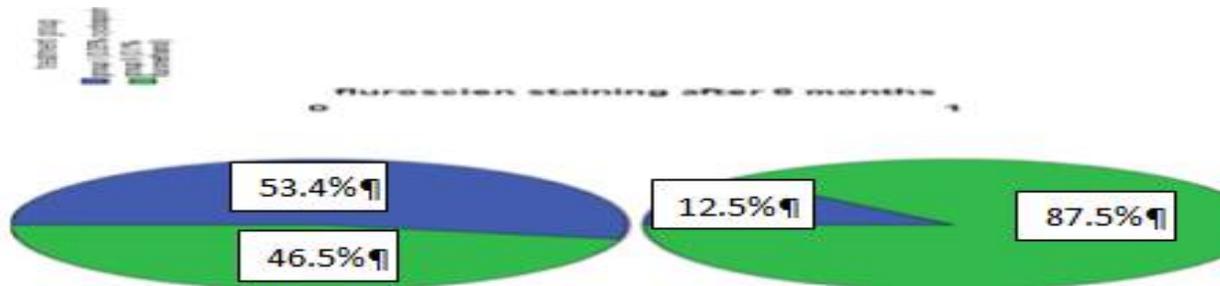**Figure-1: Gender wise distribution in both treatment groups.**

Figure-2: Comparison of fluorescein staining between two treatment groups.

keratitis, VKC, bacterial and fungal keratitis, glaucoma, punctal plug placement, punctal occlusion and vitreo-retinal diseases were excluded from the study.

Similarly patients with systemic diseases like diabetes mellitus, hypertension, pregnant and lactating patients were also excluded.

Total 94 patients fulfilling the criteria were included in the study through non-probability puposive sampling and randomly divided in two equal groups of 47 patients by utilizing WHO sample size calculator for two means taking confidence interval of 95%[1]. A prior approval

0.1% fluromethalone eye drops and standard topical lubricant. Topical lubricant in both groups was the same (systane eye drops).

Tear breakup time in seconds was taken as interval between last blink and appearance of first dry spot on the cornea after fluorescein staining while viewing with cobalt blue filter on slitlamp biomicroscope (Topcon).

Schirmer test was performed without local anesthesia with Whatmann filter paper No. 35 having dimensions of 35 mm x 05 mm. The paper was folded 5mm and inserted in lower conjunctival sac for 5 min and then amount of wetting measured.

Fluorescein staining was noticed while viewing in cobalt blue filter of slitlamp biomicroscope (Topcon) in mainly three areas i.e. nasal conjunctiva, temporal conjunctiva and cornea. One point was assigned to each area.

All pretreatment and post treatment values of dry eye disease patients were categorized in four grades of severity according to ITF guidelines.

Grade I being mild and grade IV being very severe keratocojunctivitis sicca.

All the data were entered and analyzed using statistical package for social sciences (SPSS) version 20. Mean and standard deviation were calculated for quantitative variables (tear break up time, schirmer test, fluorescein staining and age). The *p*-value was calculated from independent sample t-test for quantitative variables. Frequency and percentage were calculated for qualitative variables (gender and severity of keratoconjunctivitis sicca). The chi-square test was used to develop association between two qualitative variables of group. The *p*-value <0.05% was considered significant.

All the patients were followed up after interval of 03 and 06 months.

RESULTS

In this study a total of 94 patients (n=47) were enrolled, among these 18 were male and 29 were female patients in each treatment group (fig-1). The age range was 42 to 78 years in both groups with mean age of 62.31 (SD ± 7.7) years. Both groups were comparable in respect of age and gender.

The mean tear breakup time (BUT) in group I (cyclosporine) was 5.15 (SD ± 1.76) seconds while in group II (fluromethalone) it was 5.55 (SD ± 1.92) seconds. After 06 months trial mean BUT in group I was 12.13 (SD ± 1.49) seconds as compared to group II mean BUT was 10.72 (SD ± 2.06) seconds showing earlier tear break up in group II as compared to group I. The *p*-value is 0.007 (*p*<0.05) showing statistically significant increase in tear break up time (BUT) in patients

treated with topical cyclosporine (group I) as compared to patients treated with topical fluromethalone (group II) as shown in table.

The mean value of schirmer test in group I at start of study was 5mm (SD ± 1.79 mm) as compared to 5.36 mm (S.D ± 1.85 mm) in group II at start of study. After 06 months trial, the mean value of Schirmer test score was12.38 (S.D ± 1.66 mm) in group I as compared to mean Schirmer test score of 11.30mm (S.D ± 2.32mm) in group II indicating increased tear production in group I patients treated with topical cyclosporine. The *p*-value is 0.01 (*p*<0.05) which is statistically significant in this outcome variable.

The mean fluorescein staining in group I was 2.04 (S.D ± 0.69) at start of study comparable with group II mean fluorescein staining 2.02 (S.D ± 0.67). At the end of study the fluorescein staining was much reduced in group I with a mean value of 0.02 (S.D ± 0.14) as compared to group II the mean value was 0.15 (S.D ± 0.36). The *p*-value was also statistically significant *p*=0.027 (*p*<0.05) as shown in fig-2.

In group I atstart of the study 12 (25.53%) patients were in grade II KCS, 24 (51.06%) in grade III KCS and 11 (23.40%) were in grade IV KCS. At end of the study in group I treated with topical cyclosporine there were 42 (89.36%) patients were in grade I KCS, 5 (10.63%) in grade II KCS and none in grade III KCS & IV KCS.

In group II treated with topical fluromethalone at start of the study 16 (34.04%) patients were in grade II KCS, 22 (46.80%) patients in grade III KCS and 9 (19.14%) patients in grade IV KCS. At end of the study in group II there were 26 (55.31%) patients in grade I KCS, 19 (40.42%) in grade II KCS, 2 (4.25%) in grade III KCS and none in grade IV KCS (fig-3). The *p*–value =0.001 which is also statistically significant. Showing better results for group I treatment in all outcome parameters.

DISCUSSION

The data analysis showed favorable increase in BUT time in group I treated with topical

cyclosporine (p-0.007). Similarly in schirmer test which is marker for dry eye disease, the tear production increased in group I as shown by increased schirmer test score (mean value 12.38 mm ± 1.66) as compared to group II schirmer test score (mean value 11.30 ± 2.32).

Similar results were also reported by Stephen C, Pflugfelder. They reported an increased schirmer test score in 59% of patients

treated with 0.05% cyclosporine in various countries of world[3,5,6,9].

Furthermore the laboratory investigations on conjunctival cells and corneal epithelium while on treatment with 0.05% cyclosporine to increase conjunctival goblet cells density, decreased expression of immune activation markers, apoptosis markers and inflammatory cytokines. The number of CD[3,4,8] positive T-lymphocytes in

Table: Comparison of tear break up time in group I (cyclosporine treated) and group II (fluromethalone treated).

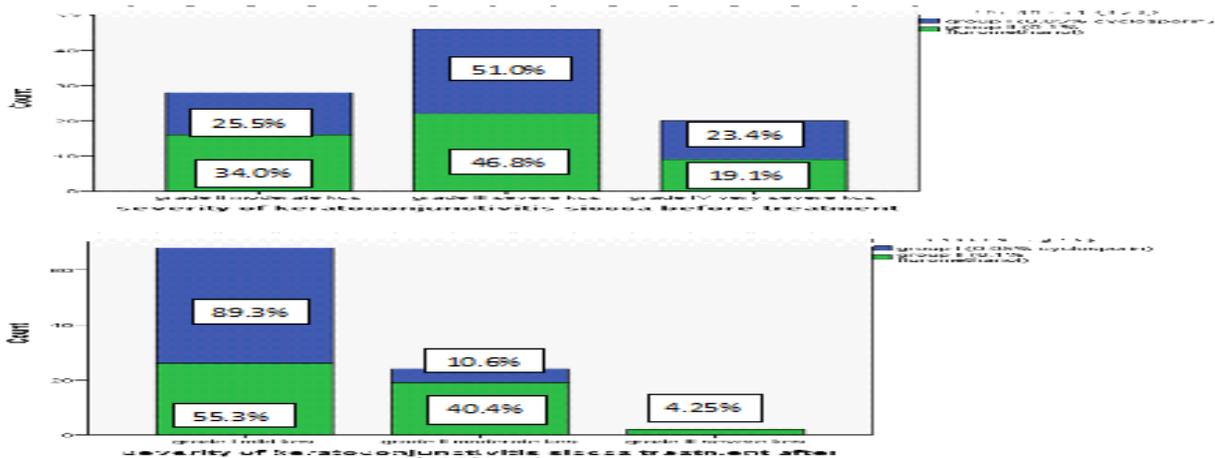| Tear break up time in seconds	Treatment group	No. of cases (n)	Mean	Std. Deviation	*p*-value
Baseline	group I (0.05% cyclosporin)	47	5.15	1.769	0.291
	group II (0.1% fluromethanol)	47	5.55	1.920	
3 months	group I (0.05% cyclosporin)	47	8.62	1.895	0.042
	group II (0.1% fluromethanol)	47	8.26	2.027	
6 months	group I (0.05% cyclosporin)	47	12.13	1.498	0.007
	group II (0.1% fluromethanol)	47	10.72	2.061	

Figure-3: Comparison of keratoconjunctivitis sicca severity before and after treatment in both groups.

having an increase of 10 mm or more as compared to 4% of control subjects. The treatment with cyclosporine 0.05% also produced significantly greater improvements ($p<0.05$) in three subjective measures of dry eye disease i.e. blurred vision symptoms, need for concomitant artificial tears and the global response to treatment[1].

Numerous studies have found the favorable outcome in dry eye disease parameters when

the conjunctiva is decreased in cyclosporine treated eyes[11-14].

In our study at the end there were 89.36% patients in grade I (mild) KCS in group I (0.05%cyclosporin) as compared to 55.31% patients in grade I (mild) KCS in treatment group II (0.1% fluromethanol) clearly showing the greater number of patients improved to grade I (mild) KCS in group I (89.36%) as compared to group II (55.31%). The *p*-value was 0.001 ($p<0.05$)

which is statistically significant there by proving our hypothesis that group I treatment (topical cyclosporine) was superior in effects as compared to group II treatment (topical fluromethalone) in management of dry eye disease.

CONCLUSION

In conclusion the dry eye disease treatment with 0.05% cyclosporine was more effective in improving KCS as compared to the conventional treatment with steroids like 0.1% fluromethalone.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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