Research Article

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Effectiveness of a Preservative-Free Eye Drop, Cyclosporine 0.05% Emulsion, and Omega-3 Supplementation as a Fixed Combination in Dry Eye Disease - a Pilot Study

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Abstract

Purpose: We aim to evaluate the impact of combining a preservative-free drop, cyclosporine 0.05% emulsion, and omega-3 oral supplementation on the signs and symptoms of dry eye in a typical ophthalmic practice.

Design: A retrospective case series conducted on patients with dry eye disease.

Methods: Patients diagnosed with dry eye in a typical ophthalmology practice were initiated on a fixed combination regimen which included a preservative-free eye drop (I-DROP® PUR GEL, I-MED pharma), cyclosporine 0.05% ophthalmic emulsion, and oral omega-3 supplement (Dry Eye Omega Benefits®, PRN) for 3 months consecutively. The primary outcome measured was a symptom score using the Canadian Dry Eye Assessment Tool (CDEA). Secondary outcome measure was Non-invasive Keratograph Break-up Time (NIK BUT). Primary and secondary outcomes measured at baseline and 3 months following intervention were compared.

Results: Thirty-six patients were included with a female male ratio of 2.6:1 and average age of 64. Patient symptoms improved significantly following the intervention as demonstrated by a lower CDEA score during the second visit compared to the first visit (16.11 vs. 19.50, respectively) ($p < .05$). NIK BUT scores were also significantly improved as demonstrated by a higher score during the second visit compared to the first in both the right (13.18 vs. 11.44) ($p < .05$) and left (14.62 vs. 12.78) ($p < .01$) eyes, respectively.

Conclusion: A fixed combination of preservative-free eye drops, cyclosporine 0.05% and omega-3 supplementation may be an effective first line treatment option in alleviating symptoms and improving signs of patients suffering from dry eye.

Keywords: Dry Eye Disease; Artificial tears; Cyclosporine; Omega 3

Abbreviations: DED: Dry Eye Disease; DEC1: Dry Eye Clinic 1, DEC2: Dry Eye Clinic 2; CDEA: Canadian Dry Eye Assessment Tool; NIK BUT: non-invasive keratograph tear break up time; CVD: Cardiovascular Disease

Introduction

Dry eye disease (DED) affects millions of people worldwide. It is estimated that the prevalence of dry eye disease varies anywhere between 6% and 25% of a population, making it one of the most commonly treated disorders by ophthalmologists [1-5]. Age has also been shown to be associated with an increased prevalence of DED [2]. With an increasing elderly population, DED will present an increasing health care burden for treating ophthalmologists.

The pathophysiology of DED is multifactorial, ultimately caused by either decreased tear production and/or excessive evaporation of tears usually associated with ocular surface inflammation and increased osmolarity of the tear film [6]. With aging, repeated episodes of subclinical inflammation often leads to disruption of the tear film, and/or structural damage to the meibomian glands and/or the secretory ducts of the lacrimal glands [7]. Other risk factors in the development of DED include contact lenses, certain medications, certain ophthalmic surgeries, and low humidity environments. Signs and symptoms of DED include dryness of the eyes, irritation, a gritty or foreign body sensation, blurred vision, or photosensitivity. The symptoms of moderate to advanced DED are often very debilitating and may affect the quality of life to the same degree as patients with moderate to severe angina or chronic psoriasis [8].

While the underlying etiology of DED may be complex, the lack of a standardized approach has led to a variety of treatment options being described in the literature. Artificial tear drops are often the first, and only, knee-jerk reaction in the treatment of DED. Unfortunately, most artificial tear drops that are available over-the-counter contain preservatives. These preservatives have been shown to further aggravate ocular surface inflammation and yield to more DED symptoms [9,10]. Cyclosporine eye drops have proven to be an effective means of reducing ocular inflammation, irritation, and other dry eye symptoms [11-13]. The mechanism by which cyclosporine treats DED is via inhibition of T-cell mediated inflammation and by increasing tear production and goblet cell density [14-16]. Oral omega-3 supplementation has also been shown to be an effective means of reducing DED signs and symptoms [17,18]. One study suggests that the symptomatic relief provided by using omega-3 for treating DED was due to the reduction of inflammation and the improvement in meibomian gland function [17].

Although preservative-free artificial tears, cyclosporine, and omega-3 supplementation have demonstrated some efficacy in treating DED individually [9,11-13,17,18], the purpose of this study was to evaluate the efficacy of a fixed combination of all three drugs in a standardized first line approach for all DED patients that present to a dry eye clinic.

Methods

This retrospective case series set out to study all patients of either gender referred to a dry eye clinic with symptomatic DED. Inclusion criteria included any patient who demonstrated DED symptoms, regardless of severity, duration or etiology. Exclusion criteria included patients who were pre-treated with any prior dry eye treatment of any kind in the preceding one month prior to their first visit, allergy/sensitivity to any of the components of the treatment combination, patients who failed to complete their follow up regimen, patients who demonstrated non-compliance in their follow up visits, and patients who discontinued their combination therapy for reasons other than non-compliance. Thirty-six patients who met the inclusion and exclusion criteria were included in this retrospective case series. The combination treatment protocol consists of preservative free artificial tears (I-DROP® PUR GEL, I-MED pharma) four times a day, cyclosporine 0.05% emulsion eye drops twice a day, and 1 g of omega-3 supplements (Dry Eye Omega Benefits®, Physician Recommended Nutraceuticals) once daily for three consecutive months.

Primary outcome measured was a DED symptomology assessment via the Canadian Dry Eye Assessment (CDEA). The CDEA has been validated as a means of assessing DED symptomatology [19]. Secondary outcome measurements included tear break up time measured via a non-invasive keratograph with the Oculus Keratograph® 5M and any reported adverse events. Non-invasive tear break up time has been validated as a means of objectively measuring DED severity [20]. All patients were assessed at their first baseline visit (DEC1) and their 3-month visit (DEC2) using the CDEA and non-invasive keratography.

Results

Baseline demographic data is listed in Table 1. A total of 36 patients were evaluated in this study with an average age of 64 and a female to male ratio of 2.6:1. 50% (18/36) of our patients had a history of cataract surgery. The most common systemic disease in this cohort was cardiovascular disease (CVD) at 47.2% (17/36).

Table 1: Comparison of Mean Age and Sex Ratio by Patient Subgroup

	Number of Patients	Mean Age	Female:Male
All Patients	36	64.33	26:10
< 65 years old	19	55.68	17:2
≥ 65 years old	17	74.00	9:8
Males	10	71.00	0:10
Females	26	61.77	26:0
Cataracts	18	72.44	10:8
No Cataracts	18	56.22	16:2
CVD	17	71.88	9:8
No CVD	19	57.58	17:2

Table 2: Comparison of Means of NIKBUT and CDEA Scores From DEC1 Visit and DEC2 Visit

	DEC1			DEC2		
	N-OD	N-OS	CDEA	N-OD	N-OS	CDEA
All patients	11.44*	12.78*	19.50*	13.18*	14.62*	16.11*
< 65 years old	10.55	13.25	18.63*	12.71	13.65	12.89*
≥ 65 years old	12.42	12.25**	20.47	13.72	15.71**	19.71
Males	12.02	12.30**	15.70	15.68	17.77**	14.70
Females	11.21	12.97	20.96*	12.22	13.41	16.65*
Cataracts	11.81	12.35*	20.28	14.21	15.21*	18.61
No Cataracts	11.06	13.21	18.72*	12.16	13.96	13.61*
CVD	12.88	12.93*	18.00	14.65	15.30*	18.24
No CVD	10.17	12.65	20.83*	11.87	14.01	14.21*

Table 3: Comparing the Difference in Means of N-OD, N-OS, and CDEA in DEC2 Visit Verses DEC1 Visit by Subgroup

	<65 years old	≥ 65 years old	Male	Female	Cataracts	No cataracts	CVD	No CVD
N-OD	2.15	1.29	3.66	1.01	2.4	1.09	1.79	1.71
N-OS	0.40*	3.45*	5.47**	0.44**	2.93	0.75	2.37	1.37
CDEA	-5.74	-0.76	-1.00	-4.31	-1.67	-5.11	0.24*	-6.63*

Results listed in table 2 demonstrate that a fixed combination of preservative-free artificial tears, cyclosporine 0.05% emulsion, and oral omega-3 supplementation for the treatment of DED showed an improvement in both primary and secondary outcome measures. There were no reported adverse events. There was a statistically significant improvement in mean CDEA score for all patients in comparing DEC1 (mean score 19.50) versus DEC2 visit (mean score 16.11) ($p < 0.05$, paired t-test). In addition to a qualitative improvement of DED symptomology, there was also an overall trend of improvement in their quantitative measure of non-invasive keratograph tear break up time (NIKBUT) (Table 2). DEC1 baseline NIKBUT scores were 11.44 and 12.78 in the right and left eyes, respectively. DEC2 NIKBUT scores were 13.18 and 14.62 in the right and left eyes, respectively. This translated to a statistically significant improvement in net NIKBUT scores in all patients of 1.74 and 1.44 in the right and left eyes, respectively ($p < 0.05$, paired t-test).

A paired, two-tailed, t-test comparing means from N-OD, N-OS, and CDEA from DEC1 to N-OD, N-OS, and CDEA from DEC2, respectively. Abbreviations: DEC1: Dry Eye Clinic visit 1; DEC2: Dry Eye Clinic visit 2; N-OD: NIKBUT for right eye; N-OS: NIKBUT for left eye; CVD: cardiovascular disease; * $p < 0.05$; ** $p < 0.01$.

Certain subgroups demonstrated a greater benefit on fixed combination therapy for their DED symptomology (Table 2). Patients below the age of 65 had a statistically greater improvement in their CDEA scores at DEC1 (18.63) compared to DEC2 (12.89), respectively ($p < 0.05$). In addition, the female demographic reported a statistically greater improvement in their CDEA scores at DEC1 (20.96) compared to DEC2 (16.65), respectively ($p < 0.05$).

Other subgroups demonstrated a greater benefit on fixed combination therapy for their DED on their quantitative tear film metrics (Table 2). Patients over the age of 65 had a statistically significant increase in their DEC1 NIKBUT score (left eye, 12.25) compared to their DEC2 NIKBUT score (left eye, 15.71) ($p < 0.01$). The male demographic also had a statistically significant increase in their DEC1 NIKBUT score (left eye, 12.30) compared to their DEC2 NIKBUT score (left eye, 17.77) ($p < 0.01$).

The improvement in both study metrics, CDEA and NIKBUT, was demonstrated in all patients, independent of their past ocular history of cataract surgery, or past medical history of CVD. This is illustrated further when

comparing both subgroups (Table 2). Patients with a history of cataract surgery showed statistically net NIKBUT improvement between DEC1 and DEC2 of 2.92, ($p < 0.05$). Patients without a history of cataract surgery demonstrated a statistically significant CDEA score improvement from 18.72 at DEC1 to 13.61 at DEC2 ($p < 0.05$). Patients with a history of CVD demonstrated a statistically significant improvement with NIKBUT scores of 12.93 in DEC1 vs. 15.30 at DEC2 ($p < 0.05$). Patients without a history of CVD demonstrated a statistically significant improvement in CDEA scores of 20.83 to 14.21 in DEC1 versus DEC2, respectively ($p < 0.05$).

In an intra-cohort analysis certain subgroups demonstrated a greater benefit to fixed combination therapy in the treatment of DED (Table 3). Patients older than 65 demonstrated a statistically significant greater improvement than patients younger than 65 in their net NIKBUT scores, 3.45 versus 0.45, respectively ($p < 0.05$). The male demographic also demonstrated a statistically significant greater improvement in their NIKBUT scores compared to the female cohort, 5.47 versus 0.44, respectively ($p < 0.01$). Patients without CVD demonstrated a statistically significant better CDEA score compared to those with CVD, -6.63 versus 0.24, respectively ($p < 0.05$). No difference was seen between the averages of patients with or without a history of cataract surgery.

A two-sample, t-test comparing the differences in NIKBUT and CDEA scores between groups based on a demographic variable. Abbreviations: N-OD: NIKBUT for right eye; N-OS: NIKBUT for left eye; CVD: cardiovascular disease; * $p < 0.05$; ** $p < 0.01$.

Discussion

Although preservative-free artificial tear eye drops, cyclosporine 0.05% emulsion, and omega-3 supplementation have demonstrated a benefit individually in the treatment of DED [8-13], there has been no study to date that evaluates the efficacy of all three in a fixed combination.

A previous study treated DED with cyclosporine eye drops and a mixture of different ratios of omega-3/omega-6 supplementation only in contact lens wearers, but without the use of preservative-free artificial tears. The results of this study showed significant improvement in both DED symptoms and objective measures of NIKBUT [21]. Our study differs from this cohort by generalizing the DED population by including all types of DED patients irrespective of underlying etiology, duration, or co-

morbidities, and by adding a preservative-free artificial tear to the fixed combination regimen. The results of our study demonstrated that a combination of all three treatments improved symptoms as evident by the CDEA scores, and also quantitative measures as evident by improved NIKBUT scores in all patients.

Overall, this study affirms a statistically significant improvement in both qualitative and quantitative measures of DED, namely improvements in CDEA and NIKBUT. However, these results were not entirely consistent in the subgroup analysis across all cohorts (Table 2). For example, patients under the age of 65, females, and patients without a history of cataract surgery or CVD all showed significant improvements only in CDEA scores between visits, whereas patients over the age of 65, males, or those with a history of cataracts or CVD showed significant improvements only in their NIKBUT scores. This may be explained by the relatively small sample size. Furthermore, although females have a higher prevalence of DED [2], they may also be over-represented in our study cohort. As a result, their response as a cohort to the fixed combination therapy may be driving the overall results of the study. This is further illustrated by the fact that the subgroups showing the most significant CDEA improvement were the female demographic.

Interestingly, the two subgroups of patients that are older than 65 and those that are post-cataract surgery, both considered risk factors for more aggressive DED, demonstrated an improvement in NIKBUT scores. This further suggests that fixed combination therapy may be beneficial regardless of underlying etiologies or risk factors for DED. However, given the small sample size this warrants further investigation.

Limitations of this study include the retrospective methodology, small sample size, and disproportionate female to male demographic. A prospective, double-masked, placebo controlled study may further expand on our understanding of the effect of fixed combination therapy in DED and perhaps lend itself to a more individualized approach to therapy. In conclusion, the use of preservative free artificial tear drops, cyclosporine 0.05% emulsion, and omega-3 supplements in a fixed combination are an effective first line treatment in DED.

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