·Clinical Research·

A randomized controlled trial of omega-3 fatty acids in dry eye syndrome

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Abstract

• AIM: To evaluate the role of dietary supplementation of omega-3 fatty acids in dry eye syndrome.

• METHODS: A prospective, interventional, placebo controlled, double blind randomized trial was done at two referral eye centers. Two hundred and sixty-four eyes of patients with dry eye were randomized to receive one capsule (500mg) two times a day containing 325mg EPA and 175mg DHA for 3 months (omega-3 group). The omega-3 group was compared to a group of patients (n=254) who received a placebo (placebo group). There were 4 patient visits (at baseline, 1 month, 2 months and 3 months). On each visit, recording of corrected distance visual acuity (CDVA), slit lamp examination and questionnaire based symptom evaluation and scoring was done. A symptomatic score of 0-6 was mild, 6.1-12 moderate and 12.1-18 severe dry eye. Response to intervention was monitored by routine tear function tests like Schirmer I test, tear film break-up time (TBUT), Rose Bengal staining and most notably, conjunctival impression cytology.

• RESULTS: Sixty-five percent of patients in the omega-3 group and 33% of patients in placebo group had significant improvement in symptoms at 3 months (P=0.005). There was a significant change in both Schirmer´s test value and TBUT values in the omega-3 group (P<0.001), both comparisons. However, there was a larger drift in TBUT values in omega-3 than the placebo group, in comparison to Schirmer´s test values. The mean TBUT score was 2.54±2.34 in the omega-3 group and 0.13±0.16 in placebo group, respectively. The mean reduction in symptom score in omega-3 group was 2.02±0.96 as compared to 0.48±0.22 in placebo group (P<0.001). Despite a slight increase mean score, the Schirmer scores did not correlate well with symptomatic improvement.

• CONCLUSION: Omega-3 fatty acids have a definite role for dry eye syndrome. The benefit seems to be more marked in conditions such as blepharitis and meibomian gland disease. The role of omega fatty acids in tear production and secretion needs further evaluation.

• KEYWORDS: dry eye syndrome; omega-3 fatty acids; conjunctival impression cytology; meibomian gland disease

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INTRODUCTION

Dry eye syndrome (DES) is a multifactorial disease, affecting tears and the ocular surface. It is accompanied by increased osmolarity of tear film, and inflammation of the ocular surface [1-3]. Despite recent advances in understanding the etiopathogenesis of DES, there remain a lacuna in diagnosis, prevention and definitive treatment[4].

DES is a common problem worldwide and can reduce the working efficiency of an individual. Dry eye is therefore a frequent reason that patient present to eye care clinics. Common patient's complaints related to dry eye include reduced vision, difficulty reading, difficulty driving at night and difficulty doing computer work[5].

Most diagnostic tests for dry eye are poorly standardized, making compare between studies tenuous at best. A generally agreed upon 'gold standard' still does not exist. Additionally, some of these tests are poorly associated with subjective symptoms[6,7].

Artificial tear supplementation is the most common therapy for dry eye. However, artificial tears provide only temporary and incomplete symptomatic relief and may not reverse metaplastic changes [8]. Hence, DES has been the subject of important and interesting research over the past few decades. Therapeutic regimens such as extracellular Uridine tri-phosphate, androgen hormones and tear replacements containing recombinant forms of cytokine growth factors are currently under evaluation[9-11].

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and alpha linolenic acid (ALA) are the three Omega-3 fatty acids that cannot be synthesized in the body and have to be supplemented in diet. EPA and DHA modulate prostaglandin metabolism towards anti-inflammatory prostaglandin synthesis due to competitive inhibition of the arachidonic acid pathway [12]. Inflammation plays a significant role in DES. For example, increased concentrations of cytokines such as interlukin-1, interlukin-6, and tumor necrosis factor-alpha have been found in the tear film of dry eye patients[13].

The geographical terrain in the plains and foothills of the northern part of the sub-continent has dry, windy conditions with high exposure to ultraviolet radiation. Moreover, semi-urban diets are devoid of food of animal origin particularly, fish.

The present study assessed whether modification of diet with omega-3 fatty acids could improve symptoms and clinical parameters of disease activity and of note, ultra-structural changes in patients with DES.

SUBJECTS AND METHODS

Subjects A prospective, interventional, randomized, double blind study was conducted at two referral eye centers. The institutional review boards and the local ethics committee approved the trial. A written informed consent was obtained from all patients based on Helsinki protocol.

Inclusion criteria were: age over 16 years of age with symptoms of dry eye; fluorescein tear film break-up time (TBUT) less than 10s and; the presence of lid margin scaling, telangiectasia, collarette and meibomian gland plugging on slit-lamp examination.

Exclusion criteria were: any pre-existing ocular disease other than DES; patients on oral tetracycline or corticosteroids and; past history of herpetic eye disease, liver disease, diabetes or laser *in situ* keratomileusis (LASIK). Other exclusion criteria included pregnancy, or lactating mothers, cognitive or psychiatric disorder, post-menopausal women, HIV and Hepatitis B and C. Patients with inability to swallow soft gel capsules. Patients on aspirin or anti-coagulant therapy, allergy to fluorescein, patients with a malignancy or chronic infection of the lacrimal gland were also excluded from the study. Topical medications and contact lens usage was discontinued prior to intervention.

Methods

Randomization and sample size calculation Patients were enrolled on the basis of a questionnaire with common symptoms of dry eye. A pilot study was first done on 20 subjects. The mean decrease in symptoms score in test group was 0.63 and 0.56 in placebo group respectively. The common standard deviation was 0.32. Assuming 1:1 randomization, alpha was set at 0.05 and power 80%. The estimated sample size of each sample was calculated to be 259 (www.stat.ubc.ca/~rollin/stats/ssize/n2.html). Figure 1 shows the patient flow chart, randomization schedule and follow-up protocol.

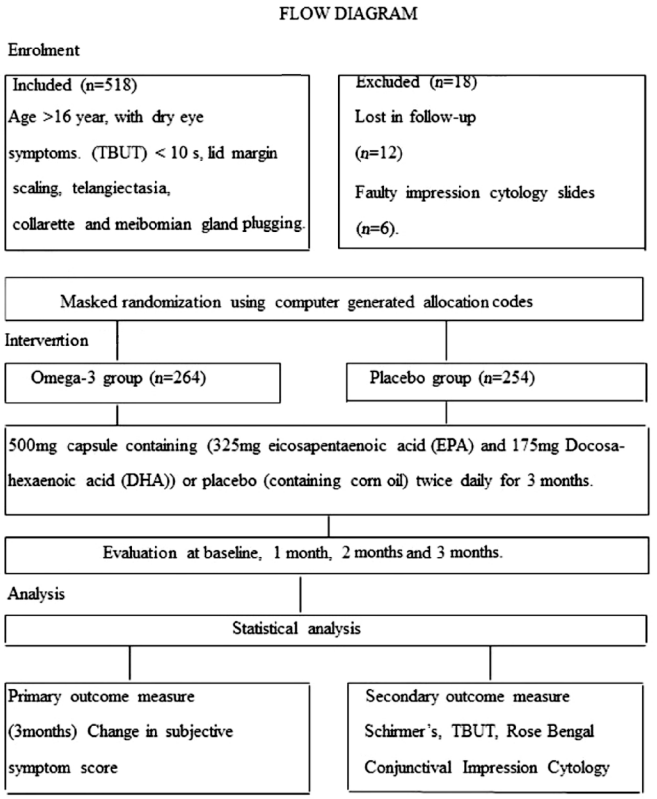

Figure 1 Flow chart for enrollment, randomization, intervention, follow−up and analysis.

Patients were randomly assigned to one of two groups by parallel assignment. The allocation codes were generated by a DOS based computer software. The allocation was concealed in green colored envelopes that were opened by health care staff not involved in patient care. Group 1 received dietary omega-3 supplementation (omega-3 group) whereas Group 2 received a placebo (placebo group). The two types of capsules and packs were similar to each other (omega-3 dietary supplementation). Currently, there is no universally accepted dosing schedule for omega-3 fatty acids for DES. However, due to safety concerns and the potential for cumulative toxicity, patients were given either one 500mg capsule twice daily containing [325mg eicosapentaenoic acid (EPA) and 175mg Docosahexaenoic acid (DHA)] or placebo capsule (containing corn oil) daily for 3 months in a pack containing 60 capsules. The subjects were masked to the contents. They were instructed to return the bottles at the one month visit. At one month, another bottle with 60 capsules was provided to the subjects.

The primary outcome measures (3 months after intervention) were the change in subjective symptoms of dry eye. A score of 0-3 was assigned to the common symptoms of dry eye such as itching or burning, sandy or gritty sensation, redness, blurring of vision, ocular fatigue or excessive blinking,

respectively. When absent (0), sometimes present (1), frequently present (2), and always present (3) . (Score of 0-6 was mild, 6.1-12 moderate and 12.1-18, severe dry eye)[14].

The secondary outcome measures (3 months after intervention) were the Schirmer's Ⅰ test for tear production, TBUT, the Rose Bengal score (RBS) as a measure of ocular surface integrity and conjunctival impression cytology (CIC) scores for cellular changes and goblet cell density.

Subjects were seen at baseline, 1 month, 2 months and 3 months after beginning the supplementation. At each visit, each subject underwent a detailed ocular examination by an independent investigator (not a study ophthalmologist, HP). This included measurement of best corrected visual acuity (BCVA) and slit lamp biomicroscopy. Slit lamp examination included assessment of the lid margins, eye lashes and meibomian gland orifice for any blockage or stenosis. A questionnaire of dry eye symptoms was provided at every visit and scores assigned for each symptom (Table 1). Platelet count, prothrombin time and activate partial thromboplastin time (APTT) were also measured at each visit.

TBUT was first performed as manipulation of the eyelids may affect the results. Two successive readings were performed and averaged. The subject then waited for 30min, and Schirmer's test with anesthesia was performed with eyes closed. The subject waited for another 30min and the Rose Bengal test was performed with the hanging drop method. A van Bijsterveld score of 4 or more was considered positive for dry eye[15].

CIC was performed with the eye anaesthetized with one drop of 4% xylocaine. Then the lacrimal lake at inner canthus was dried with a cotton tip applicator. A filter paper was grasped with blunt smooth edge forceps and applied to the temporal bulbar conjunctiva. The filter paper was gently pressed with a glass rod held in the other hand. The paper strip was removed in a peeling fashion after 4-10s and a specimen transferred to the lab for staining and fixation. The filter paper was placed on a glass slide with albumin paste for specimen transfer. The slide was labeled and numbered. It was stained with Periodic acid-Schiff (PAS) and counter stained with haematoxylin and eosin.

The mounted slide was examined under a microscope with 10X high power field (HPF). After localization, cells were then examined under 40X HPF for goblet cells and epithelial cells. At least 10 HPF were examined. Grading and scoring was recorded based on the criteria suggested by Nelson [16]. Grades 0 and 1 were normal and Grades 2 and 3 were abnormal.

Statistical Analysis Statistical analysis was performed with Pearson Chi-square test. Means between groups were compared using the t-test. P values were calculated at 1% and 5% confidence interval for Chi-square tests and 95% confidence interval for the $t$test respectively. A P value of less than 0.001 at 1% and 95% confidence interval was statistically significant.

RESULTS

Totally 518 patients (eyes) participated in the study. Two hundred and sixty-four eyes were randomized to omega-3 group and 254 eyes to placebo group. Twelve patients were lost in follow up and 6 were excluded from the study due to faulty impression cytology slides.

There were 268 females and 254 males in the placebo and omega-3 groups combined (P=0.289). The mean age in Omega-3 group was 38.82±4.12 years and 40.06±6.76 years in placebo group respectively (P=0.218).

At last visit (3 months), 65% of the symptomatic patients were asymptomatic and 35% had moderate improvement in symptoms in the omega-3 group. By 3 months, 33% of the symptomatic patients were asymptomatic and 67% had moderate improvement in symptoms in the placebo group. The symptomatic to asymptomatic conversion rate was statistically significant (P=0.005).

The change in the subjective symptoms score was compared in the omega-3 and placebo groups. On t-test, in the omega-3 group, the mean subjective symptom score was 2.02±1.96 and the standard error of mean was 0.14 (Table 1). In the placebo group, the mean was 0.18 ±0.22 and the standard error of mean was 0.03.

On t-test, in the omega-3 group, the mean Schirmer's was 0.62 ±1.06 and the standard error of the mean was 0.10 (Table 2). In the placebo group, the mean was 0.14±0.35 and standard error of mean was 0.05. The difference between groups was statistically significant (P<0.001).

In the omega-3 group, the mean TBUT was 2.54±2.34s and the standard error of mean was 0.22s. In the placebo group, the mean TBUT was 0.13 ±0.16 and the standard error of mean was 0.02s (Table 3). The difference between groups was statistically significant (P<0.001).

The outcomes of tear function tests (Schirmer's, TBUT, RBS and CIC) on day 1 and at completion (day 90), were compared. Chi-square test was used to establish the strength of association. RBS had a statistically significant relation at the 1% level (P<0.001) for the omega-3 group and a statistically insignificant relation at the 1% level (P=0.564) for the placebo group (Table 4).

There was no statistically significant association in the placebo group for CIC scores (P=0.250). However, a statistically significant association (P<0.001) was present in the omega-3 group (Table 5).

Day 1 and day 90 comparisons in TBUT profile was also significant (P<0.001) (Table 6).

Outcome measures were also evaluated for etiologies of dry eye. In Sjögren's syndrome there was no change in Schirmer's test values at day 1 and day 90 in both groups. TBUT values, RBS and CIC scores were also similar between groups at 3

Table 1 Change in symptoms score post-intervention

Change in symptoms score	*n*	Mean	SD	Min	Max	*t*-test
Omega-3 group	264	2.02	0.96	1.48	2.46	
Placebo Group	254	0.48	0.22	0.36	0.56	
Total	518	1.25	0.59	0.92	1.51	0.000

SD: ±Standard deviation; Std. Error: Standard error; Min: Minimum; Max: Maximum.

Table 2 Schirmer's test values post-intervention

Change in Schirmer's value	*n*	Mean	SD	Min	Max	*t*-test
Omega-3 group	264	0.62	1.06	0.42	0.82	
Placebo Group	254	0.14	0.35	0.08	0.20	
Total	518	0.38	0.82	0.27	0.49	0.000

SD: ±Standard deviation; Std. Error: Standard error; Min: Minimum; Max: Maximum.

Table 3 Change in TBUT values post-intervention

Change in TBUT value	*n*	Mean	SD	Min	Max	*t*-test
Omega-3 group	264	2.54	2.34	2.11	2.98	
Placebo group	254	0.13	0.16	0.10	0.16	
Total	518	1.33	2.05	1.07	1.60	0.000

SD: ±Standard deviation; Std. Error: Standard error; Min: Minimum; Max: Maximum; TBUT: tear film break-up time.

Table 4 Rose Bengal score comparisons

RBS score		Omega-3 group			Total	Placebo group			Total
		0-4	4.1-6	6.1-9		0-4	4.1-6	6.1-9	
Day 90	0-4	134	8	0	142	146	2	0	148
	4.1-6	45	37	0	82	14	76	0	90
Day 1	6.1-9	0	26	14	40	0	0	16	16
Total		179	71	14	264	160	78	16	254

On Chi-Square tests, *P* values in test and Placebo group were 0.000 and 0.564 respectively. RBS: Rose Bengal score.

Table 5 Conjunctival impression cytology scores comparisons

CIC score	Omega-3 group			Placebo group		
	Normal	Abnormal	Total	Normal	Abnormal	Total
Day 90	176	0	176	166	0	166
	68	20	88	50	38	88
Day 1	244	20	264	216	38	254

On Chi-square test, *P* values in test and Placebo group were 0.000 and 0.250 respectively; CIC: Conjunctival impression cytology.

Table 6 Tear film break up time comparisons *n* (%)

Group	TBUT day 1			Total	TBUT day 90			Total
	>10.1s	5.1-10s	<5s		>10.1s	5.1-10s	<5s	
Omega-3	28 (10.6)	174 (66)	62 (23.4)	264 (100)	89 (33.7)	135 (51.1)	40 (15.1)	264 (100)
Placebo	128 (50.4)	110 (43.3)	16 (6.3)	254 (100)	140 (55.1)	100 (39.4)	14 (5.5)	254 (100)

TBUT: Tear film break-up time. *P* values in test and Placebo groups were 0.000 and 0.000 respectively.

months. The McNemar test indicates that there was no statistically significant relationship between the variables.

In contact lens users, there was no significant change in Schirmer's test values in both the groups. However, there was significant improvement in TBUT values, RBS and CIC scores in the test group at 3 months. (P=0.005)

In video display terminals (VDTs) group, the Schirmer's test values were similar between groups at 3 months. In the placebo group there was no improvement in the TBUT scores in 87.8% eyes compared to 57.69% subjects in the omega-3 group (P=0.250). CIC scores in both groups were similar at 3 months.

In chronic blepharitis cases, there was a slight difference in Schirmer's values between groups. Twenty percent of the subjects in the omega-3 group had abnormal values as compared to 38% in the placebo group at 3 months. The most striking difference was seen in TBUT results. In omega-3 group, 90.47% of subjects had an improved TBUT score compared to 18.75% of subjects in placebo group(P<0.001). For subjects with acne rosacea, the Schirmer's test values

were similar in both groups at 2 months. However, 50% patients had an improved TBUT at 2 months as compared to 33% in the placebo group.

DISCUSSION

Rosenberg and Asbell[17] recently performed an analysis of all currently published literature on omega-3 fatty acids and dry eye disease and found that although correlation exists between essential fatty acids supplementation and dry eye disease, strong conclusions still cannot be made because of limitations in research reported.

To explore the hypothesis that omega-3 fatty acids will cause improvement in symptoms and clinical parameters DES, we conducted a multi-centric, prospective, interventional, randomized, double blind placebo controlled trial in Northern India, where diets are devoid of omega-3 fatty acids. This was in contrast to the Eastern and Southern parts of the sub-continent where fish is an essential component of diet.

Mounting evidence, accumulated over the past decade, has shown a potential benefit of Omega-3 fatty acids on the eye, particularly in macular disease [18,19]. Polyunsaturated fatty acids modulate the arachidonic acid pathway and influence the inflammatory response in disease states. Omega-3 fatty acids cannot be produced the body and need to be supplemented by diet. EPA and DHA have an anti-inflammatory action in contrast to omega-6 fatty acids which are pro-inflammatory[20].

The FDA has established an acceptable daily intake (ADI) of 3g (3 000mg) per person of combined EPA and DHA from natural fish oil sources in either oil or capsule form but only under a physician's supervision, since intakes above 3g (3 000mg) per day may cause excessive bleeding in some people. The recommended daily intake (RDI) and recommended dietary allowance (RDA) have still not been established for EPA and DHA.

There was a slight preponderance of females in our study. This could be explained by the fact that acne rosacea, keratoconjunctivitis sicca and meibomian gland disease are more common in females probably due to different levels of androgens and dietary supplementation[21].

At 3 months post-intervention, there was an improvement in symptoms score, (Table 2) in both groups, however there was a significant improvement in the test group. Creuzot and colleagues also observed improvement of dry eye relative to symptoms in a placebo controlled randomized trial in a small sample size of subjects [22]. Miljanovic *et al* [23] assessed the diets of 32 470 women and found that those with higher omega-3 fatty acids consumption had decreased risk for dry eye. Our study indicates that omega-3 supplementation induces changes in the ocular surface as there was an improvement in CIC scores in the test group which was statistically significant (P<0.001) in contrast to the placebo group (P=0.250).

In the test group there was a statistically significant improvement in the TBUT scores at 3 months (from baseline) as compared to placebo. This result was similar to a randomized trial by Macsai and colleagues in which TBUT as well as meibum score changed significantly from baseline at one year[24].

There has been some evidence that inflammation reduces aqueous tear production and T-cell inhibitors such as topical cyclosporine increase Schirmer scores. However, in the present study, we found a smaller drift in Schirmer scores in both groups and a slight increase in overall average. Of note, there was a lack in correlation between symptomatic improvement and the Schirmer score.

This result was in contrast to a pilot study by Wojtowicz *et al* [25] in which there was increase in tear production and volume. The difference in findings between studies could be due to the small sample size in their study (n=36).

In patients with Sjögren's syndrome, there was no improvement in primary and secondary outcome measures in both omega-3 and placebo groups. These findings were in contrast to a randomized clinical trial in on 38 women with Sjögren's syndrome with improvements in clinical parameters and symptoms score [26]. However, this study could not differentiate between evaporative and aqueous deficient dry eye. A possible explanation of this observation could be that long-standing inflammation of ocular surface results in irreversible changes in the lacrimal glands.

The significant drift in the symptoms and TBUT scores in the omega-3 group suggest that dietary supplementation with omega-3 fatty acids improves the inherent stability of tear film as compared to tear production.

This observation was reinforced by the reduced aqueous tear evaporation rate and improved CIC scores in the omega-3 group. This difference was more marked in patients with meibomian gland disease and chronic blepharitis where 90.47% patients had improved TBUT scores in the omega-3 group as compared to only 18.75% in the placebo group. This finding was also supported clinically by reduction in the number of blocked meibomian ducts and improvement in meibomitis in the omega-3 group.

It is likely that dietary supplementation of omega-3 fatty acids alters the composition of meibomian gland secretions and meibum quality in patients with meibomian gland disease and chronic blepharitis. However, we did not attempt to study meibum characteristics in the present study.

Recent advances in understanding the pathophysiology of DES has lead to evolution of newer modalities of treatment. Omega-3 fatty acids modulate the inflammatory process in the body and nutritional supplementation may have a promising role to play in dry eye.

Dietary intervention with omega-3 fatty acid not only causes symptomatic improvement but betters clinical markers of dry

eye as seen by a positive drift in primary and secondary outcome measures. There is a likely improvement in inherent stability of the tear film as seen by the larger TBUT drift and CIC scores. However, these tests are not a specific marker for any subtype of dry eye and further studies of changes in meibum quality and quantity may broaden the usefulness of omega-3 fatty acids.

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