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Oral omega-3 fatty acids treatment in computer vision syndrome related dry eye

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ABSTRACT

Purpose: To assess the efficacy of dietary consumption of omega-3 fatty acids (O3FAs) on dry eye symptoms, Schirmer test, tear film break up time (TBUT) and conjunctival impression cytology (CIC) in patients with computer vision syndrome.
Setting and design: Interventional, randomized, double blind, multi-centric study.
Methods: Four hundred and seventy eight symptomatic patients using computers for more than 3 h per day for minimum 1 year were randomized into two groups: 220 patients received two capsules of omega-3 fatty acids each containing 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA) daily (O3FA group) and 236 patients received two capsules of a placebo containing olive oil daily for 3 months (placebo group). The primary outcome measure was improvement in dry eye symptoms and secondary outcome measures were improvement in Nelson grade and an increase in Schirmer and TBUT scores at 3 months.
Results: In the placebo group, before dietary intervention, the mean symptom score, Schirmer, TBUT and CIC scores were 7.5 ± 2, 19.9 ± 4.7 mm, 11.5 ± 2 s and 1 ± 0.9 respectively, and 3 months later were 6.8 ± 2.2, 20.5 ± 4.7 mm, 12 ± 2.2 s and 0.9 ± 0.9 respectively. In the O3FA group, these values were 8.0 ± 2.6, 20.1 ± 4.2 mm, 11.7 ± 1.6 s and 1.2 ± 0.8 before dietary intervention and 3.9 ± 2.2, 21.4 ± 4 mm, 15 ± 1.7 s, 0.5 ± 0.6 after 3 months of intervention, respectively.
Conclusion: This study demonstrates the beneficial effect of orally administered O3FAs in alleviating dry eye symptoms, decreasing tear evaporation rate and improving Nelson grade in patients suffering from computer vision syndrome related dry eye.
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1. Introduction

Dry eye syndrome is public health problem affecting vision related quality of life. Recently, there have been significant advances in our understanding of the dry eye pathogenesis; ocular surface inflammation is now considered to be an integral part of dry eye disease [1].

Ocular surface health may be influenced by hormones, contact lens wear, refractive surgeries, humidity, medications, smoking and computer work [2–5].

Role of personal computers has increased exponentially in all spheres of life (school, office and home). Almost everyone including children, college students, software professionals and the elderly are hooked on to the computers every day, ranging from 2 to 12 h; use of mobile phones further add to the overall burden. Prolonged visual display terminal tasks reduce blink rate, blink amplitude and blink quality leading to tear film instability [6,7]. People experience one or more symptoms referred to as computer vision syndrome; these include eye strain, tired eyes, headache, burning of eyes, redness, foreign body sensation, blurring of vision, sometimes accompanied by backache and neck pain; visual symptoms predominate in 64–90% patients [8–10].

Artificial tear supplements are commonly used to treat dry eye in computer users; although, these supplements provide symptomatic relief, they do alter the pathophysiology of dry eye [11–13].

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Table 1
Dry eye questionnaire and scoring system (DESS©).

Symptom	Score (maximum 18)			
	Absent (0)	Sometimes (1)	Frequent (2)	Always present (3)
Itching or burning				
Sandy or gritty sensation				
Redness				
Blurring of vision				
Ocular fatigue				
Excessive blinking				

Scores of 0–6 were mild, 6.1–12 were moderate, and 12.1–18 indicated severely symptomatic dry eye [17]. © Bhargava R. Laser Eye Clinic, Noida, India.

O3FAs are anti-inflammatory and have proven to be effective in conditions like rheumatoid arthritis and coronary artery disease [14]; moreover, some studies have reported increased tear production in dry eye patients following dietary supplementation of fish oil and flaxseed oil for 3 months [15].

Some authors are of the opinion that the ratio of O6FA to O3FA determines the overall inflammatory status of the body; a cross sectional study by Miljanović et al. in a large series of patients (Women Health Study) found that a higher ratio of O6FA to O3FA consumption was associated with a significantly increased risk of dry eye disease in women [16].

However, safety and efficacy of O3FAs for dry eye in computer users has not been established. An extensive review of literature (Medline search) revealed that no randomized trial has been done to determine this.

The present study hypothesize that oral O3FA supplementation does improve dry eye symptoms, limbal cytology and morphology (as seen on CIC) as well as clinical markers like Schirmer test and TBUT in symptomatic computer users when compared to administration of placebo (olive oil).

2. Methods

A prospective, multi-centric, randomized, double blind interventional study was done at Rotary Eye Hospital, Palampur, Laser Eye Clinic, Noida and Santosh Medical College, Ghaziabad, which are referral eye centres in northern part of Indian subcontinent. The trial was approved by the institutional review boards and the local ethics committee. A written informed consent for the study, based on Helsinki protocol was obtained from all the participating patients.

2.1. Inclusion criteria

A survey (questionnaire based) was conducted in regional IT parks, call-centres, regional medical schools and universities. Symptomatic computer users (using computers for >3 h/day for minimum 1 year) were identified and invited to take part in the trial. The patients were enrolled on the basis of a questionnaire of dry eye related symptoms (Table 1) (Dry Eye Scoring System, DESS©) [17].

2.2. Exclusion criteria

Patients having current ocular infection, past history of laser in situ keratomileusis (LASIK), allergic conjunctivitis, contact lens wear, herpetic eye disease, diabetes, liver diseases were excluded. Other exclusion criteria included pregnancy or lactating mothers, HIV and Hepatitis B and C. Patients with inability to swallow soft gel capsules, on aspirin or anti-coagulant therapy, and those allergic to fluorescein were also excluded. Systemic (tetracycline's and corticosteroids) or topical medications (other than artificial tear supplements) that could affect tear film or meibomian gland functions were discontinued prior to intervention. However, patients were instructed not to use artificial tear preparations, 2 h prior to testing.

2.3. Randomization, masking and sample size calculation

To calculate the sample size to compare the mean difference in symptom scores between the two groups, a pilot study was first done on 20 subjects. The mean decrease in symptoms score in O3FA group was 0.83 and in placebo group 0.69, respectively. The common standard deviation was 0.47. Assuming 1:1 randomization, alpha was set at 0.05 and power 90%. The estimated sample size in each group was 237. Fig. 1 shows the patients flow chart, randomization schedule and follow up protocol.

Patients were randomly allocated to one of the two groups by parallel assignment. The allocation codes were generated by a DOS based software in the Department of Community Ophthalmology. The codes were sealed in blue coloured envelopes and were opened by health care personnel not involved in patient care. O3FA group received two 300 mg capsules containing each containing 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA), twice daily for 3 months. Placebo group received two capsules containing olive oil, twice daily for 3 months. The subjects as well as the investigators were masked to the contents. The two types of capsules and packs were similar to each other. Patient compliance was assessed by health care personnel (not involved in

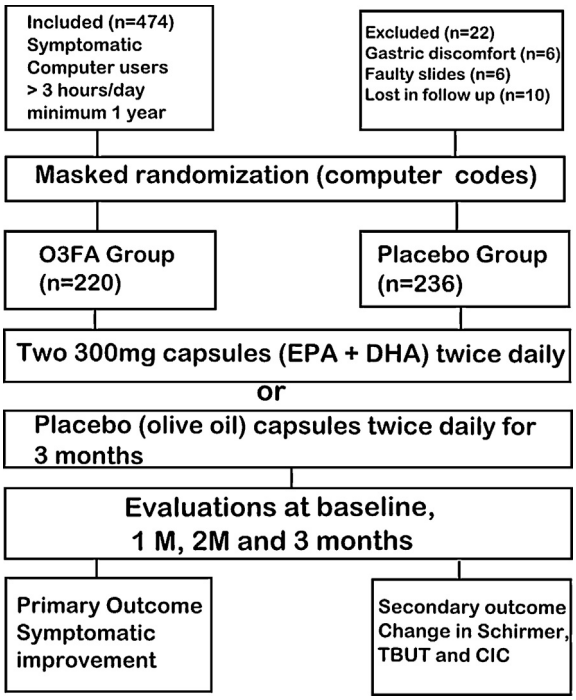

Fig. 1. Flow chart for enrolment, randomization, intervention, analysis and follow up.

patient care); the subjects were instructed to return the bottles at each monthly visit, the number of capsules returned (if any) were counted, and another pack with 120 capsules was provided to them. The subjects were instructed to take a normal diet, and not to take additional dietary supplements.

3. Outcome measures

Patients were seen at baseline, 1 month, 2 months and 3 months after the start of dietary supplementation. The primary outcome measure was decrease from baseline in subjective dry eye symptoms at 3 months post-intervention. A score of 0–3 was assigned to dry eye related symptoms like ocular fatigue, blurring of vision, itching or burning, sandy or gritty sensation and redness respectively (DESS©). When absent (0), sometimes present (1), frequently present (2), and always present (3). A score of 0–6 was mild, 6.1–12 moderate and 12.1–18, severely symptomatic dry eye (Table 1).

The secondary outcome measures (3 months after start of dietary supplementation) were change in Schirmer test value (tear production), TBUT (measure of tear film stability) and Nelson grade (for cellular morphology and goblet cell density).

4. Ocular examination and tear function tests

At each visit, the subjects underwent a detailed ocular examination by an independent investigator (SK), who was not a study surgeon. This included recording of corrected distance visual acuity (CDVA) and slit lamp examination for the assessment of lid margins, eye lashes, and meibomian gland orifice for any blockage or occlusion.

One eye of each patient was selected at random for evaluation; the subjects underwent Schirmer test, TBUT, and CIC. Furthermore, the subjects were given dry eye questionnaire at each visit. The independent investigator (SK) was masked to the information obtained from the questionnaire.

TBUT was first performed as eyelid manipulation may adversely influence the results. Three readings were taken in succession and averaged. The subject then waited for 30 min and Schirmer's test with anaesthesia was done with eyes closed.

The eye was anaesthetized with one drop of 4% xylocaine. The lacrimal lake at inner canthus was dried with a cotton tip applicator. A circular 0.22 micron filter paper measuring 13 mm in diameter (Sartorius, Gottingen, Germany) was grasped with a blunt tipped forceps and applied over the inferior bulbar conjunctiva. The paper strip was gently pressed with a glass rod held in the other hand. The filter paper was removed in a peeling fashion after 4–10 s and specimen transferred to the lab for staining and fixation (ethyl alcohol, formaldehyde, and glacial acetic acid in 20:1:1 volume ratio). The filter paper was placed on a glass slide with albumin paste for specimen transfer. The slide was labelled and numbered, and then it was stained with periodic acid-Schiff and counterstained with haematoxylin and eosin. The mounted slide was first examined under the light microscope with 100× low power field (10× objective lens). After localization, cells were then analyzed with 400× final magnification (40× objective). At least 10 HPF (10 different regions of the slide) were examined for goblet cells and epithelial cells as use of a small sampling area (high power field of view) is likely to result in an unacceptably large uncertainty (variability) in GCD estimates [18]. Grading and scoring was carried out by criteria suggested by Nelson [19]. Nelson grades 0 and 1 were regarded as normal, whereas grades 2 and 3 were considered to represent abnormal cytology.

Table 2
Mean baseline characteristics of patients.

Parameter	Omega 3 group	Placebo group	*P* value (*t* test)
Age (years)	22.8 ± 2.5	23.7 ± 6.8	0.134
Symptom score	8 ± 2.6	7.5 ± 2	0.028
Schirmer's score (mm)	20.1 ± 4.2	19.9 ± 4.7	0.632
TBUT (s)	11.7 ± 1.6	11.5 ± 2	0.238
CIC	1.2 ± 0.8	1 ± 0.9	0.013
GCD (cells/mm^2)	890 ± 336	875 ± 383	0.652

Abbreviations: TBUT, tear film break up time; TBUT, tear film break up time; CIC, conjunctival impression cytology; GCD, goblet cell density.

Table 3
Mean test values at 3 months after dietary intervention.

Parameter	Omega 3 group	Placebo group	*P* value
Symptom score	3.9 ± 2.2	6.8 ± 2.2	<0.001
Schirmer score (mm)	21.4 ± 4	20.5 ± 4.7	<0.008
TBUT (s)	15 ± 1.8	12 ± 2.2	<0.001
Nelson Grade	0.5 ± 0.6	0.9 ± 0.9	<0.001
GCD (cells/mm^2)	1018 ± 281	899 ± 375	<0.001

Abbreviations: TBUT, tear film break up time; TBUT, tear film break up time; CIC, conjunctival impression cytology; GCD, goblet cell density.

5. Statistics

Statistical analysis was performed on an intent to treat basis using SPSS software for windows (version 22, IBM Inc.). Means of groups were compared using t tests. Chi-square tests were used for proportions. A P value <0.05 was considered statistically significant.

6. Results

Of 478 subjects recruited, 22 were lost to follow-up. Of the remaining subjects, 220 had been assigned to the O3FA group and 236 to the placebo group. Four hundred and fifty six patients completed the 3 months follow up. Gastric intolerance to O3FAs (n = 6), faulty impression cytology slides (n = 6) and inability to return for follow up visits (n = 10) were the main reasons for dropout. Overall, 219 males and 237 females participated in the study.

Table 2 shows that mean test values at baseline were comparable in O3FA and placebo groups. Table 3 shows mean test values 3 months after start of dietary intervention.

Fig. 2 shows the comparison between the percentage of patients with dry eye symptoms at inclusion and after 3 months of dietary intervention in both groups, respectively.

The change in subjective symptom score was compared in the O3FA and placebo groups. Fig. 3 shows the comparisons between mean symptom score, Schirmer, TBUT and Nelson grade at baseline and after 3 months of dietary intervention. There was a significant improvement in symptoms (P < 0.001), Schirmer (P = 0.008), TBUT (P < 0.001) and Nelson grade (P < 0.001) in O3FA group; the main cytological feature being presence of smaller cells with both polygonal and round shape and increase in goblet cell counts. The change was not significant in the placebo group (Table 3).

In the O3FA group, 32.9% patients had abnormal Schirmer in comparison to 30.7% patients in the placebo group at baseline. In O3FA group, 54.8% patients had abnormal TBUT as compared to 56.3% patients in the placebo group at baseline. Similarly, 35.5% patients in O3FA group had abnormal cytology (Nelson grades 2 and 3) as compared to 33.8% patients in the placebo group at baseline.

7. Discussion

A randomized, placebo controlled double blind trial was done in northern part of the Indian sub-continent; the typical north Indian diet is predominantly vegetarian (deficient in O3FAs); fish

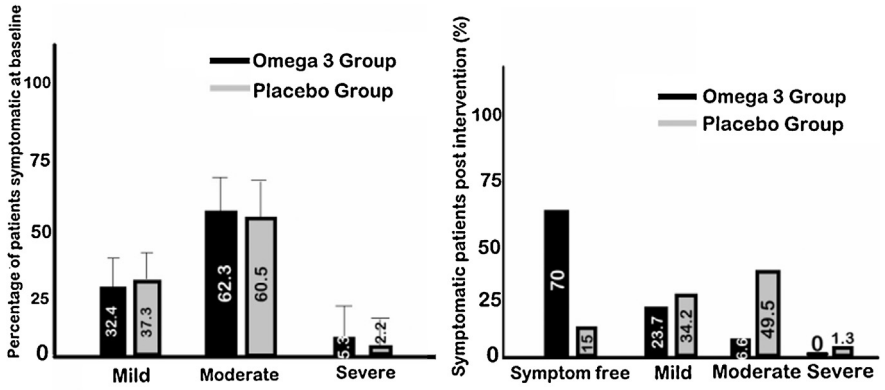

Fig. 2. Bar chart depicting percentage of symptomatic patients at baseline and at 3 months after dietary intervention.

(especially cold water fish) is not an essential dietary component as compared to diet of costal and southern India. Having said this, common Indian fishes like Rohu, Catla, Pangas and Magur have a significantly lower O3FA content in comparison to Salmon, Tuna, Sardines and Mackerel [20]. On the contrary, small quantities of omega 3 alpha linoleic acid (ALA) obtained from dark green leafy vegetables and soybean oil in vegetarians are unlikely to provide acceptable O3FA levels in these subjects.

The rampant use of personal computers and Internet has led to an increase in dry eye symptoms in young and middle aged individuals and office going population [21].

The absence of a universally accepted gold standard test for dry eye evaluation has led to a shift towards symptom based assessment as a key component of clinical diagnosis [22]. Moreover, dry eye symptoms and signs observed are discordant; patient may not be symptomatic despite abnormal tear function tests and not all symptomatic patients have abnormal tear function tests [23]. This was reinforced by observation in present study that amongst symptomatic computer users, 33% had abnormal Schirmer's, 55% had abnormal TBUT and 35% abnormal cytology at baseline in both groups combined.

One of the most important features of dry syndrome is alteration of conjunctival and corneal epithelium as seen on vital staining. However, these methods do not indicate degree of squamous metaplasia or changes in goblet cell density. Therefore, in the present study, we used CIC as a direct indicator of ocular epithelial damage and subsequent improvement after start of dietary supplementation.

Although dryness of eye has been more prevalent among elderly women; in present study, preponderance of dry eye symptoms in young patients highlight the increasing impact computers in causing dry eye disease [24].

O3FA dietary supplementation significantly reduced symptoms in O3FA group (4 ± 2.8) as compared to placebo group (0.7 ± 1.4);

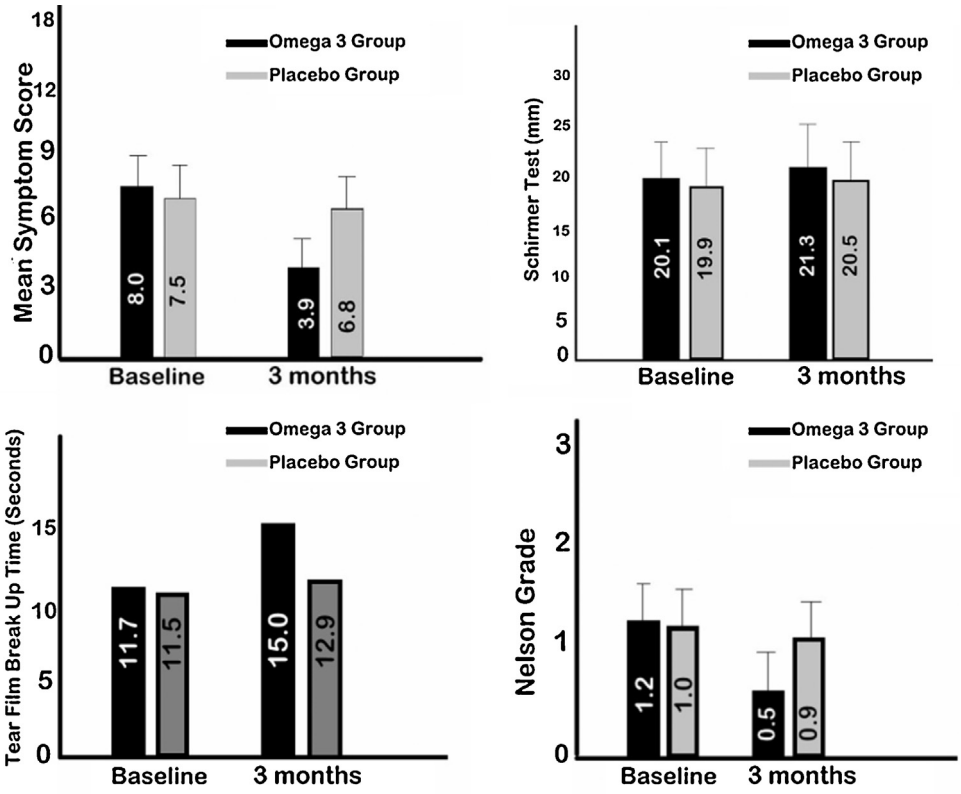

Fig. 3. Bar chart depicting dry eye symptoms and tear film characteristics (Schirmer, TBUT and Nelson Grade) at baseline and at 3 months after dietary intervention.

seventy percent patients were totally symptom free in contrast to 14.9% patients in the placebo group at conclusion. In a double blind clinical trial, Kangari et al. found that even short term ($n = 30$ days) consumption of O3FAs was associated with improvement in dry eye associated symptoms [25].

At 3 months, mean Schirmer's score improved from baseline in both the groups (1.2 ± 1.2 versus 0.6 ± 0.8 mm); however, the magnitude of improvement was relatively small ($P = 0.008$). In a large series of patients ($n = 518$), a randomized, double blind trial by Bhargava et al. also found a smaller drift in Schirmer test scores following O3FA dietary supplementation for 3 months [26]. However, another randomized controlled trial by Wojtowicz et al. found increased tear production and tear volume following dietary intervention with omega 3 fatty acids for three months. Small sample size of patients this study ($n = 36$) could explain for the difference in observation [15].

There was a significant improvement in TBUT in O3FA group at 3 months. A mean increase in TBUT of 3.2 ± 1.8 s was seen in O3FA group in contrast to 0.4 ± 0.6 s in placebo group ($P < 0.001$). Nelson grade improved significantly from baseline in the O3FA group as evidenced by increased goblet cell counts and smaller polygonal epithelial cells.

In a double-masked, randomized, controlled trial assessing the effect of oral supplementation of O3FA and O6FA on a conjunctival inflammatory marker in dry eye patients, Brignole-Baudouin et al. found reduced expression of HLA-DR marker on flow cytometry of CIC samples (an anti-inflammatory effect) with improvement in dry eye symptoms [27].

The significant improvement in dry eye symptoms and TBUT scores in O3FA group suggests that O3FA dietary supplementation improves inherent tear film stability rather than increasing tear volume and production. This observation was further reinforced by decreased tear evaporation rates improved Nelson grade in O3FA group.

Thus in conclusion, dietary consumption of O3FAs causes significant improvement in dry eye symptoms, decreases tear evaporation rate and better Nelson grade, as evidenced by increased goblet cell density and improved epithelial cellular morphology.

Conflict of interest

None.

Financial interest

We do not have any financial interest.

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