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To Study The Effects of Omega 3 Fatty Acids In Patients With Meibomian Gland Dysfunction : A Randomised , Prospective Controlled Study

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Abstract
***Aim**: To evaluate the role of Omega 3- fatty acids in patients with Meibomian gland dysfunction.*
***Methods**: A Prospective, interventional , placebo controlled, randomized study was done at Department of Ophthalmology, Rajindra Hospital , Patiala. Fifty (50) patients with Meibomian gland dysfunction fulfilling the inclusion criteria excluding the exclusion criteria were randomized into two groups – Group A and Group B containing 25 patients each. Group A patients treatment included cleaning the lid margins with neutral baby shampoo and use of artificial tears without preservatives, plus oral supplementation with one capsule (500 mg) two times a day containing 325mg EPA and 175mg DHA for 3 months. Group B patients treatment included cleaning the lid margins with neutral baby shampoo and use of artificial tears without preservatives, plus a placebo oral agent. for 3 months. Patients were followed in OPD at day 0 , 1 month , 2 month and 3 month. At every visit , slit lamp examination (severity of lid margin inflammation , meibomian gland secretion) , OSDI (ocular surface index) and routine tear function test : Schirmer I test , tear film break-up time (TBUT) and Rose Bengal staining were performed. Data was collected and evaluated using unpaired –t test statistical analysis.*
***Results**: After 3 months of evaluation, the mean OSDI, TBUT and Rose Bengal staining presented significant improvement from the baseline values in Group A (p value< 0.001, p value<0.001 and p <0.05 respectively) as compared to Group B. The Schirmer test results were also improved and statistically significant (p<0.05).*
***Conclusion**: Oral omega 3 fatty acids 1g per day is beneficial in the treatment of MGD .*
***Keywords**: Meibomian gland dysfunction, Omega 3 fatty acids*

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I. 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 . Meibomian gland dysfunction (MGD) is the most frequent cause of dry eye disease (DED). Eyelid inflammation, microbial growth, associated skin disorders as well as potentially severe corneal complications culminate to make MGD a complex multifactorial disorder. MGD is a heterogeneous condition arising from any combination of the following five separate pathophysiological mechanisms: eyelid inflammation, conjunctival inflammation, corneal damage, microbiological changes and DED resulting from tear film instability.[4] Generally, it is higher in Asian populations, ranging from 46% to 70%, whereas in Caucasian populations the MGD prevalence ranges from 3.5% to 20%.[5] MGD may be classified as a low- or high-delivery state, according to the extent of meibomian lipid secretion. The low-delivery state, which is the most common form of MGD, is associated with deficiencies in meibomian secretion, and it may be further characterized as obstructive, with cicatricial and non-cicatricial subcategories, or hyposecretory. Hyposecretory MGD is associated with gland atrophy. Obstructive MGD is the most prevalent form of low-delivery state MGD and is caused by hyperkeratinisation, which is influenced by sex, hormonal disturbances, topical medications and age. High-delivery state MGD, also known as hypersecretory MGD, is characterized by the release of large amounts of meibum at the lid margin in response to pressure on the eyelids. Hypersecretory MGD has been associated with seborrhoeic dermatitis in 100% of cases, but it may also be associated with rosacea.[6]

The regular treatments for MGD comprise: cleansing of the lid, use of artificial tears, topical application of corticosteroids and erythromycin, and oral tetracycline/doxycycline. Tear cytokines also play an important role in chronic inflammation in MGD, interleukin (IL)-1β, IL-7, IL-12, IL-17, and macrophage inflammatory protein-1β levels are found to be higher in the MGD patients.[10,11]Essential fatty acid supplementation has been shown to have an anti-inflammatory effect on dry eye symptoms.[12]Fish oil is a

source of long-chain omega-3 polyunsaturated fatty acids: Eicosapentaenoic acid (EPA) and Docosahexaenoic acid. The omega-3 fatty acid EPA and the omega-6 fatty acid arachidonic acid (AA) act competitively as a substrate for both the enzyme cyclooxygenase and the enzyme 5-lipoxygenase. The anti-inflammatory action is believed to result from the synthesis of prostaglandin E3 and leukotriene B5 (LTB5) from EPA that inhibits the conversion of AA to the potentially harmful inflammatory mediator's prostaglandin E2 and leukotriene B4.[13]

II. Material And Methods

This prospective, interventional and randomized study was conducted in Department of Ophthalmology, Rajindra Hospital , Patiala between January 2017 and August 2017.

Study Design: A total of 50 patients of both sexes and age between 23-85 yrs diagnosed with MGD were included in this study after fulfilling the inclusion criteria and excluding the exclusion criteria.

Inclusion Criteria: Age 23-85 yrs
Diagnosed with MGD
Willing to participate in the study

Exclusion Criteria: Age<23 or >85 yrs
Any other ocular disease other than MGD
H/O diabetes, HIV , Hepatitis, Cancer
Pregnant and lactating , Post-menopausal women
H/O pre existing herpes disease
Ophthalmic laser treatment (<3 months)
Any topical medications, multivitamin tablets and contact lens usage were discontinued atleast 15 days prior to inclusion in the study.

MGD was diagnosed by dry eye symptoms (itching, burning ,sandy or gritty sensation, redness , blurring of vision , ocular fatigue or excessive blinking) and expression of clear fluid /cloudy fluid / cloudy particulate fluid or insipissated and toothpaste –like material when the lids were pressed with fingers on slit- lamp examination. 50 Patients which were included in the study (after fulfilling the inclusion and exclusion criteria) were then randomized into two groups : Group A and Group Beach containing 25 patients . At visit 0, following baseline characters were recorded :

- Age
- Sex- Male/female
- SIGNS (OBJECTIVE SCORE) : 1)Lid margin inflammation severity : No injection / injection

2) Meibomian gland secretion – clear fluid / cloudy fluid / cloudy particulate fluid / inspissated toothpaste like.
3) Mean TBUT
4) Mean Schirmer I test
5) Rose Bengal staining grading : Grade 0/I/II/III/IV

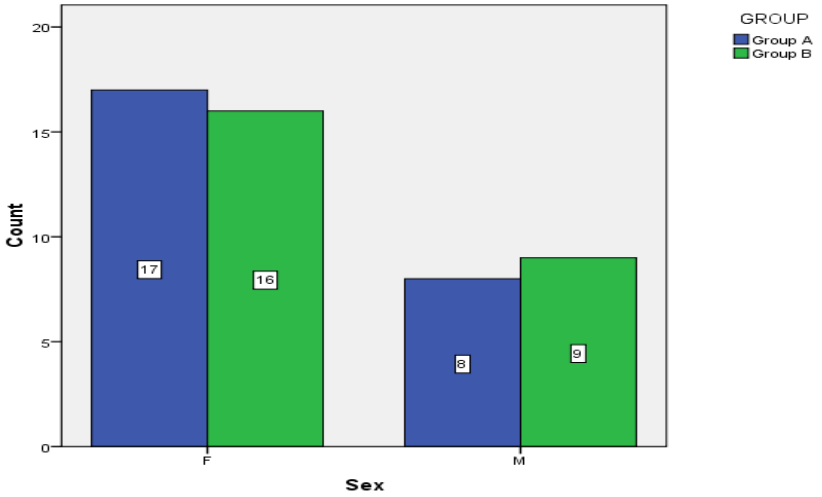
- SYMPTOMS (SUBJECTIVE SCORE) : OSDI ; normal, mild moderate , severe

Patients in both the groups were instructed regarding cleansing the lid margins with neutral baby shampoo , use of artificial tears without preservatives and an oral agent (500 twice daily). Group A patients received the oral agent which contained 325mg EPA and 125 DHA mg (Omega 3 fatty acids). Group B patients received a placebo oral agent that contained nothing but a corn oil. All the patients were masked to the contents. They were instructed to return the empty packet of tablets at every visit and new packet of tablets were given at every visit . This was done to improve the compliance.

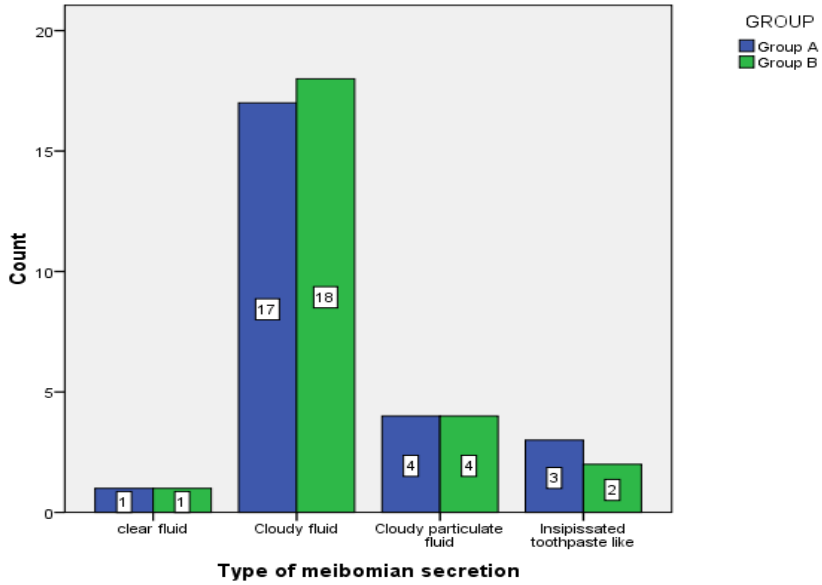
They were made to visit at the end of one month ,second month and third month and at every visit the above mentioned characterstics of every patient were recorded. TBUT was measured by instillation of one drop of 2% fluorescein. The time until appearance of the first dry spot was recorded, and the average of three trials was calculated. Schirmer test was done for 5 minutes without anaesthesia.

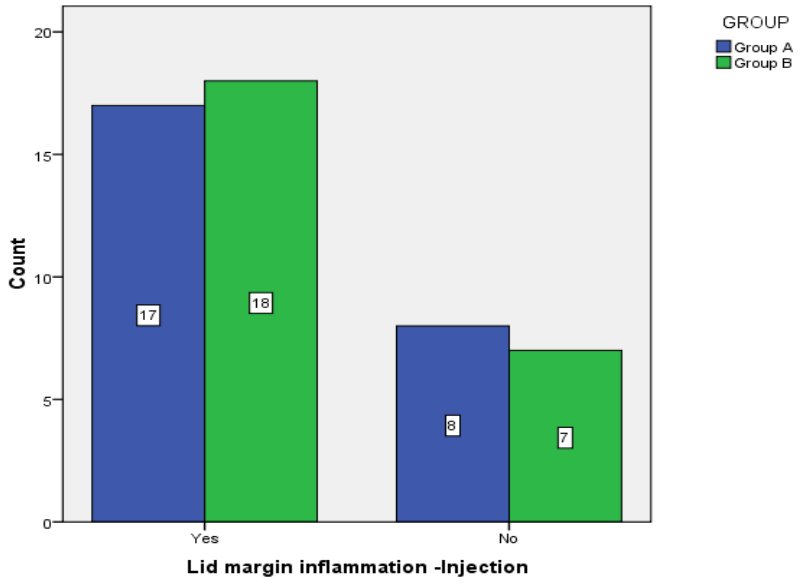
III. Results

50 Patients participated in the study. The mean age in Group A was 55.20$\pm$4.349 years and in Group B was 55.96$\pm$3.272 years. There was slight female preponderance in our study. In Group A , 17 females and 8 males and in Group B, 16 females and 9 males but there was no significant difference in the sex distribution in both the groups.



Additionally , we did not observe significant intergroup difference in baseline signs and symptoms .





Treatment response:

Schirmer`S Test: At baseline (0 day), the mean value in Group A and Group B was 6.88(2.848)mm and 7.16(2.511)mm respectively. At the end of the 3 months, mean value of Schirmer test was 17.68 (8.270)mm and 12.68 (7.244) mm in Group A and Group B respectively (p value <0.05).

	GROUP	N	Mean	Std. Deviation	P value
Schirmer test (mm) : 0 day	Group A	25	6.88	2.848	.714
	Group B	25	7.16	2.511	
Schirmer test (mm) : 1 month	Group A	25	9.92	4.242	.198
	Group B	25	8.56	3.015	
Schirmer test (mm) : 2 month	Group A	25	13.64	6.396	.116
	Group B	25	10.96	5.404	
Schirmer test (mm) : 3 month	Group A	25	17.68	8.270	.027
	Group B	25	12.68	7.244	

Osdi Test: At baseline(0 day), OSDI mean value in Group A and B was 25.76$\pm$9.107 and 24.52$\pm$6.475 respectively. At end of the 3 months , mean value in Group A and B was 7.68$\pm$5.080 and 17.36$\pm$9.425 respectively. Group A showed a significant decrease in tear dysfunction symptoms at 3 months as compared to Group B (p value < 0. 001) .

	GROUP	N	Mean	Std. Deviation	P value
OSDI : 0 day	Group A	25	25.76	9.107	.582
	Group B	25	24.52	6.475	
OSDI : 1 month	Group A	25	21.28	8.429	.869
	Group B	25	21.64	6.788	
OSDI : 2 month	Group A	25	14.96	9.021	.203
	Group B	25	18.04	7.829	
OSDI : 3 month	Group A	25	7.68	5.080	
	Group B	25	17.36	9.425	.000

Tbut Test: At baseline (0 day) , the mean TBUT was 7.28 (2.701) seconds and 6.76(2.603) seconds for Group A and B respectively. At each monitoring, the mean TBUT for Group A was greater than the baseline and Group B and there was significant difference between the groups (p<0.001).

	GROUP	N	Mean	Std. Deviation	P value
TBUT : 0 day	Group A	25	7.28	2.701	.492
	Group B	25	6.76	2.603	
TBUT : 1 month	Group A	25	8.44	2.567	.257
	Group B	25	7.64	2.361	
TBUT : 2 month	Group A	25	9.16	2.609	.281
	Group B	25	8.40	2.309	
TBUT : 3 month	Group A	25	14.32	5.089	
	Group B	25	8.72	2.458	.000

Rose Bengal Test : At baseline (0 day), the mean value of Rose Bengal staining was 5.36$\pm$ 1.823 and 5.72$\pm$1.514 in Group A and B ,respectively.At the end of 3 months, there was significant difference in mean value of Group A (2.12$\pm$2.205) as compared to Group B (3.84$\pm$1.724) . (p value = 0.003)

	GROUP	N	Mean	Std. Deviation	P value
Rose bengal staining : 0 day	Group A	25	5.36	1.823	.451
	Group B	25	5.72	1.514	
Rose bengal staining : 1 month	Group A	25	4.36	2.079	.146
	Group B	25	5.12	1.509	
Rose bengal staining : 2 month	Group A	25	3.00	2.062	.018
	Group B	25	4.28	1.595	
Rose bengal staining : 3 month	Group A	25	2.12	2.205	.003
	Group B	25	3.84	1.724	

IV. Discussion

The main cause of MGD is hyperkeratinization and its related pathogenesis (for example, ductal dilatation and acinar atrophy). Other pathologies, such as atopy, pemphigoid, acne rosacea, and seborrhea are related to MGD and may result in a chronic inflammation of the ocular surface.Thus, all these circumstances may also lead to dry eye, the alteration of the tear, and irritation of the eye shown by MGD patients.[14] The anti-inflammatory power of essential polyunsaturated fatty acids used in treatment of the ocular surface may be compared with corticosteroids, as they act as the same mediator, through nuclear factor kappa B (NF-κB) signal transduction, of the inflammation cascade.[15] Creuzot and colleagues observed improvement of dry eye relative to symptoms in a placebo controlled randomized trial in a small sample size of subjects .[16] Miljanovic assessed the diets of 32 470 women and found that those with higheromega-3 fatty acids consumption had decreased risk for dry eye.[17]

There was a slight preponderance of females in our study. This can 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.[18] At 3 months post-intervention, there was an improvement in symptoms score in both groups, however there was a significant improvement in the Group A as compared to Group B ($p < 0.001$). Also, there was significant improvement in Schirmer score , TBUT score and Rose Bengal score at the end of 3 months as compared to baseline value (p value< 0.05, $p < 0.001$, $p < 0.05$ respectively) which was statistically significant. Omega-3 fatty acids modulate the inflammatory process in the body and nutritional supplementation may have a promising role to play in dry eye.

V. 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.

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