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The Effectiveness of Lipofilm Microemulsion Eye Drops in Dry Eye Syndrome by Enhancing The Tear Film Quality

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ABSTRACT

The aim of this study was to evaluate the effectiveness of lipofilm microemulsion as ocular lubricant in dry eye syndrome. It was prospective randomized clinical trial design with single blind masked study. Sixty eyes were enrolled according to the inclusion and exclusion criteria. Two weeks and four weeks of follow-up were documented. Objective parameters were Schirmer I test and break up time test. Subjective symptoms were assessed by means of 1-10 scale of visual analogic score. Thirty eyes were enrolled to lipofilm group and 30 eyes to sodium hyaluronate 0.15% group. Both groups had improvement in mean Schirmer test ($p < 0.001$) but there was no statistically difference between two groups after two weeks ($p = 0.361$) and four weeks ($p = 0.081$). Both groups induced a significant increase of break up time test ($p < 0.001$) and there was statistically significant difference in lipofilm group after two weeks ($p = 0.037$) and four weeks ($p = 0.002$). Symptoms improved in all groups but statistically significant different in lipofilm group in foreign body sensation ($p = 0.001$) and blurred vision ($p = 0.021$) after two weeks. Lipofilm tends to show a faster improvement than sodium hyaluronate in patients with dry eye syndrome.

Key words: *lipofilm microemulsion, sodium hyaluronate, Schirmer test, break up time test, visual analogic score, dry eye syndrome.*

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INTRODUCTION

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1] Tear replacement by topical artificial tears and lubricants is currently the most widely used therapy for dry eye, and a variety of components are used to formulate a considerable number of commercially available preparations.[2] Ocular lubricant replace tear volume, and though only paliative, are frequently effective in mild dry eye syndrome.[3]

The tear lipid layer has the important function of delaying the water evaporation thus maintaining tear film stability and osmolarity.[4,5] The preservation of a stable precorneal tear film is essential for ocular surface health.[6] Several studies indicated that there is a correlation between lipid deficiency in the precorneal tear film, increased evaporation and dry eye syndrome.[7] Microemulsion lipofilm is a thermodynamically stable microemulsion of oil in water containing lipids and having a physiological function very close to that of lipid layer present in natural tears. The chemo-physical structure of the microemulsion, in particular the presence of oil droplet of sub-micron size and its stability give to Lipofilm the capability of improving the tear lipid barrier function by restoring the lipid layer as well as a wettability similar to that of natural tears.[8]

The purpose of this study is to evaluate the effectiveness of Lipofilm microemulsion compared to Sodium hyaluronate 0.15% in dry eye syndrome by enhancing the tear film quality.

Table 1. Demographic and baseline characteristic

Variable	Lipofilm group	Sodium hyaluronate group	P
Gender			
Male (N,%)	6 (50%)	6 (50%)	1.00
Female (N,%)	24 (50%)	24 (50%)	1.00
Age: years (mean±SD)	70.43 ± 7.61	68.47 ± 8.56	0.35
Schirmer I test: mm. (mean±SD)	6.20 ± 2.25	7.23 ± 3.59	0.45
BUT test: seconds (mean±SD)	6.10 ± 1.45	5.93 ± 1.20	0.52
Burning: VAS (mean±SD)	1.83 ± 2.46	2.07 ± 2.45	0.71
Foreign body sensation: VAS (mean±SD)	2.60 ± 1.80	2.77 ± 1.40	0.69
Itching: VAS (mean±SD)	3.03 ± 2.24	3.17 ± 1.90	0.80
Blurred vision: VAS (mean±SD)	1.73 ± 2.08	2.23 ± 2.34	0.39

Table 2. Changes in Schirmer I test between baseline and follow-up

Variable	Lipofilm group	Sodium hyaluronate group	p
Schirmer I test: mm (mean±SD)			
Baseline	6.20 ± 2.25	7.23 ± 3.59	
After 2 weeks	9.27 ± 3.15	9.77 ± 3.61	0.905*
Changes	3.07 ± 2.26	2.53 ± 1.80	0.361*
After 4 weeks	11.20 ± 3.27	11.00 ± 3.81	0.575*
Changes	5.00 ± 2.84	3.77 ± 2.61	0.081*

*Mann-Whitney Test

MATERIAL AND METHODS

The study followed the design of single masked randomised parallel group clinical trial. The treatment duration was 4 weeks. The study included 60 patients (60 eyes), 48 (80%) females dan 12 (20%) males, mean age 69.45 years, range 52–98 years) with dry eye syndrome defined by two clinical test: break up time test, < 10 seconds in each eye, Schirmer's I test < 7 mm wetting/5 min in each eye and at least one of the following symptoms of dry eye: burning, foreign body sensation, itching and blurred vision. Only one eye of the patients, that suffered the worst symptoms of dry eye was used for the analysis.

Inclusion criteria were patients aged > 21 years, suffered from dry eye syndrome, informed consent written. Exclusion criteria were any active inflammation of the eye, lactation and pregnancy; history of systemic contraception; history of eye trauma, infection and ocular surgery within the past 6 months before inclusion, wearing contact lens, having ocular surgery due to dry eye syndrome, such like punctum cauterisation and use of topical and/or systemic treatments potentially interfering with tear productions.

Natural tear production was assessed by the Schirmer's test, in which the extent of tear flow down a piece of filter paper inserted into the lateral part of the inferior fornix of the eye is measured over a 5 minute period. The tear film break-up time (time between last blink and first disturbance of the corneal tear film, BUT) was assessed as a measure of the stability of the preocular tear film.

Subjective symptoms (i.e. burning/pain; foreign body sensation; itching; blurred vision) were assessed by means of 1–10 scale of visual analogic score (VAS). Absence of any pain constituted a score of 0 points on the visual analog pain scales, and intense, unbearable pain was considered a full pain score of 10 points and the patients were asked to check a point on the line corresponding to their degree of pain. Lipofilm microemulsion was administered into the conjunctival sac, at least 3 times/day. As reference drug a commercially available multidose ophthalmic solution containing 0.15% Sodium Hyaluronate was used. Similarly to Lipofilm it was administered into the conjunctival sac at least 3 times/day. Each patient was assigned to one of the treatments, according to a randomisation list, and underwent to 3 visits, as reported in the following study plan: *visit 1* (baseline); *visit 2* (after 2 weeks of treatment); *visit* 3 (after 4 weeks of treatment). In each visit the following variables were collected in the following order: Schirmer I test, break up time test and subjective symptoms. These parameters were compared before, two weeks and four weeks after treatment.

Since the sample size was small and, therefore, the distribution was not normal, non parametric tests were applied (i.e. Wilcoxon's test and Mann-Whitney's test).

Table 3. Changes in break up time test between baseline and follow-up

Variable	Lipofilm group	Sodium hyaluronate group	P
Break up time test: seconds (Mean±SD)			
Baseline	6.10 ± 1.45	5.93 ± 1.20	
After 2 weeks	10.37 ± 2.34	9.10 ± 1.85	0.034*
Changes	4.27 ± 2.05	3.17 ± 1.93	0.037^0
After 4 weeks	12.67 ± 2.41	10.63 ± 1.56	0.001*
Changes	6.57 ± 2.25	4.70 ± 1.73	0.002*

*Mann-Whitney Test; ^{0}T-Test

Tabel 4. Subjective symptoms on visual analogic score between baseline and follow-up

Variable	Lipofilm group	Sodium hyaluronate group	p
Burning: VAS (mean±SD)			
Baseline	1.83 ± 2.46	2.07 ± 2.45	0.558
After 2 weeks	0.30 ± 0.88	0.77 ± 1.52	0.119
After 4 weeks	0.00 ± 3.68	0.07 ± 0.37	0.317
Foreign body sensation: VAS (mean ± SD)			
Baseline	2.60 ± 1.79	2.77 ± 1.41	0.336
After 2 weeks	0.13 ± 0.57	0.77 ± 1.10	0.001*
After 4 weeks	0	0	1
Itching: VAS (mean ± SD)			
Baseline	3.03 ± 2.24	3.17 ± 1.89	0.414
After 2 weeks	0.30 ± 0.59	0.70 ± 1.26	0.300
After 4 weeks	0	0	1
Blurred vision: VAS (mean ± SD)			
Baseline	1.73 ± 2.08	2.23 ± 2.34	0.434
After 2 weeks	0	0.20 ± 0.48	0.021*
After 4 weeks	0	0	1

*Mann-Whitney Test

RESULTS

A total 60 eyes were enrolled in this study, of which 30 eyes were enrolled to Lipofilm microemulsion group and 30 eyes to Sodium hyaluronate 0.15% group. Table 1 summarizes demographic and baseline characteristics including gender, age, mean Schirmer test, mean break up time test, and subjective symptoms that assessed with visual analogic score. There were no significant differences between two groups with regard to these baseline characteristics. The majority of the subjects in both groups were female (80%).

After 2 weeks of follow-up both groups had achieved successful in mean Schirmer I test versus baseline ($p < 0.001$) (Table 2) but no statistically different between Lipofilm microemulsion group, compared to Sodium hyaluronate 0,15% group ($p = 0.905$). Both treatments also showed a statistically significant improvement versus baseline of mean Schirmer I test test after 4 weeks of follow-up ($p < 0.001$) (Table 2), but there were no statiscally significant difference between Lipofilm microemulsion compared to sodium hyaluronate 0.15% ($p = 0.081$).

After 2 weeks and 4 weeks after treatment both groups induced a significant improvement of break up time test versus baseline ($p < 0.001$), there were also statistically significant effect at 2 weeks ($p = 0.037$) and 4 weeks ($p = 0.002$) after treatment in Lipofilm microemulsion group, compared to Sodium hyaluronate 0.15% group. (Table 3)

Subjective symptoms (Table 4) improved on the visual analogue scale with all treatments and there were statistically significant different between two groups in foreign body sensation ($p = 0.001$) and blurred vision ($p = 0.021$) after two weeks of study in Lipofilm microemulsion group.

In terms of relief from burning sensation, 90.63% reported relief after 2 weeks while using Lipofilm microemulsion compared with 76.85% on Sodium hyaluronate 0,15%, but there were no significant difference ($p = 0.084$). After 4 weeks, 100% relief from burning sensation had been reported in Lipofilm microemulsion group, compared with 98.89% on Sodium hyaluronate 0.15%, but there were no statistically significant difference ($p = 0.387$). Its about 98.19% in Lipofilm microemulsion

Table 5. Changes of subjective symptoms between baseline and follow-up

Variable	Lipofilm group	Sodium hyaluronate group	p
Burning (%)			
After 2 weeks	90.63	76.85	0.084
After 4 weeks	100	98.89	0.387
Foreign body sensation (%)			
After 2 weeks	98.19	81.06	< 0.001*
After 4 weeks	100	100	
Itching (%)			
After 2 weeks	94.38	87.15	0.095
After 4 weeks	100	100	
Blurred vision (%)			
After 2 weeks	100	94.21	0.033*
After 4 weeks	100	100	

*Mann-Whitney Test

group had statistically significant improvement from foreign body sensation after 2 weeks of follow-up compared to 81.06% on Sodium hyaluronate group ($p < 0.001$). Both groups had achieved 100% relief from foreign body sensation after 4 weeks of study.

There were 94.38% relief from itching sensation in Lipofilm microemulsion group compared with 87.15% on Sodium hyaluronate group, but there were no statistically significant difference ($p = 0.095$). Both Lipofilm and Sodium hyaluronate 0.15% group had achieved 100% relief from itching sensation after 4 weeks.

Blurred vision also statistically significant difference in Lipofilm microemulsion group, 100% improved compared with 94.21% on Sodium hyaluronate group ($p = 0.033$). After 4 weeks, 100% relief from blurred vision had been seen on both groups. No adverse event in any group was observed by the investigator or reported by the patient throughout the study. Both treatments were well tolerated, except temporally blurred vision immediately after instillation on 9 subjects in Lipofilm microemulsion group.

DISCUSSION

In this study, dry-eye symptoms were very common in women (80%) than men (20%), mean age 69.45 years, range 52–98 years. The previous study that performed in Australia by McCarty et al.[9] indicated that women were more likely to report symptoms of dry eye. The study performed in America by Moss et al.[10] indicated that the age-adjusted prevalence in men was 11.4%, which was significantly lower than the 16.7% prevalence in women. Table 1 summarizes demographic and baseline characteristics including gender, age, mean Schirmer test, mean break up time test, and subjective symptoms that assess with visual analogic score. There were no significant differences between two groups with regard to these baseline characteristics. This study indicates that compared with men, women are more likely to have dry-eye symptoms and positive dry-eye tests, including the Schirmer test and the tear film breakup test, but not statistically significant difference.

The apparent improvement in tear production in patients receiving sodium hyaluronate 0.15%, as determined by the Schirmers's test, may reflect the water retentive property of sodium hyaluronate resulting in an increased precorneal residence time of the artificial tear and increased corneal wettability[11] and reduced tear evaporation from the ocular surface.[12] Compared with Lipofim, the chemo-physical structure of the microemulsion, in particular the presence of oil droplet of sub-micron size and its stability give to Lipofilm the capability of improving the tear lipid barrier function by restoring the lipid layer as well as a wettability similar to that of natural tears.[8]

Condon et al.[13] had reported the results of the Schirmer's test show a highly significant difference between hyaluronan and saline, also study that conducted by Aragona et al.[14] had reported improvement of the Schirmer's test but no statistically significant difference between hypotonic 0.4% sodium hyaluronate and isotonic 0.4% sodium hyaluronate. In this study both Lipofilm and Sodium Hyaluronate 0.15% groups statistically significant effect in improving the Schirmer's test ($p < 0.001$), but there were no statistically significant difference between both group after 2 weeks ($p = 0.905$) and 4 weeks ($p = 0.575$).

An unstable tear film is one of the most common findings in patients with ocular irritation caused either by reduced aqueous tear production or an increase in tear evaporation. The method most frequently used to assess tear film stability is to measure the tear break-up time (TBUT), ie, the time interval between a complete blink and the first appearance of a dry spot in the precorneal tear film after fluorescein instillation.[15,16]

Aragona et al.[14] reported that the comparison of sodium hyaluronate hypotonic 0.4% (150mOsm/L) to isotonic 0.4% after 90 days administration, there were not statistically significant different of BUT test ($p < 0.05$) in each groups. The study conducted by Aragona et al.[8]

had reported the results of the BUT test that showed no significant difference between Lipofilm microemulsion and sodium hyaluronate 0.2% groups. In this study, there were significant improvement of break up time test versus baseline ($p < 0.001$) after 2 weeks and 4 weeks in both groups, there were also statistically significant effect at 2 weeks ($p = 0.037$) and 4 weeks ($p = 0.002$) after treatment in Lipofilm microemulsion group, compared to Sodium hyaluronate 0.15% group.

McDonalds et al.[17] reported significant symptoms improvement in sodium hyaluronate 1.4% group compared to polyvinyl alcohol. The study by Aragona et al.[8] had reported significant relief of burning sensation and foreign body sensation in *Lipofilm microemulsion* group compared to sodium hyaluronate 0.2% group. In this study subjective symptoms improved on the visual analogue scale with all treatments and there were statistically significant different between two groups in foreign body sensation ($p = 0.001$) and blurred vision ($p = 0.021$) after two weeks of study in Lipofilm microemulsion group, but there was no significant difference in the symptom of burning sensation and itching between two study groups.

The foremost objectives in caring for patients with dry eye disease are to improve the patient's ocular comfort and quality of life, and to return the ocular surface and tear film to the normal homeostatic state. Although symptoms can rarely be eliminated, they can often be improved, leading to an improvement in the quality of life. It is more difficult to demonstrate that topical lubricants improve the ocular surface and the tear film abnormalities associated with dry eye.[1] Most clinical studies fail to demonstrate significant correlation between symptoms and clinical test values or between the clinical test values themselves.[18,19]

In this study *Lipofilm microemulsion* does not contain any preservative, unlike Sodium hyaluronate in this study, it contain of oxidative preservative that known as stabilized oxychloro complex (SOC). When SOC is administered in the eye, it is converted into natural tear components, such as sodium and chloride ions, oxygen, and water.[20,21] Improvement at low concentrations (0.005% w/v) that are benign to the eye makes SOC an ideal ophthalmic preservative. Safety and tolerability were established in a study of 62 patients with mild to moderate dry eye who were treated with an SOC-containing product four to eight times per day for 4 weeks.[22]

No adverse event in any group was observed by the investigator or reported by the patient throughout the study. Both treatments were well tolerated, except temporally blurred vision immediately after instillation on 9 subjects in Lipofilm microemulsion group. Lipofilm microemulsion tended to show a faster improvement than did the Sodium hyaluronate in patients with dry eye syndrome.

CONCLUSION

The results of the study show a significant clinical benefit in BUT test and improvement of the symptom of foreign body sensation and blurred vision in those dry eye patients receiving Lipofilm microemulsion.

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