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Original Research Article

Clinical Efficacy of 0.05% Cyclosporine Nano-Emulsion in the Treatment of Dry Eye Syndrome Associated with Meibomian Gland at a Tertiary Care Center, Muzaffarpur,Bihar, India

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Abstract:

Objectives: The present study aimed to evaluate the clinical efficacy of 0.05% cyclosporine nano-emulsion in treating dry eye syndrome associated with meibomian gland dysfunction at a tertiary care center in Muzaffarpur, Bihar, India.

Methods: Data were collected irrespective of age and sex using the OSDI questionnaire (Ocular Surface Disease Index). The OSDI questionnaire is a 12-item survey that quickly assesses symptoms of ocular irritation in dry eye and their influence on vision-related functions. Tear volume was assessed using Schirmer's test, and tear film stability was tested using tear film breakup time (TBUT). Lissamine green staining was used to stain the conjunctiva. Lid evaluation was performed using a slit lamp to observe lid morphology, expression of meibomian glands, and blink rate.

Results: A total of 80 patients were included; 40 subjects were in the experimental group, and 40 were in the control group. The mean age was 51.76 ± 17.28 years in the experimental group and 48.96 ± 12.54 years in the control group. Comparing the mean pre-treatment (7.42 ± 2.76 seconds) and post-treatment (13.31 ± 4.12 seconds) TBUT of cyclosporine group patients, there were statistically extremely significant differences ($p<0.0001$). Similarly, the mean pre-treatment (9.56 ± 3.24 seconds) and post-treatment (12.65 ± 2.87 seconds) TBUT in the control group also showed extremely significant differences ($p<0.0001$). However, the greater mean difference was observed in the cyclosporine group (5.91 seconds) compared to the control group (3.15 seconds). Total vascular engorgement on the lid was noted in 62 (77.5%) patients. Out of 34 patients in the experimental group, vascular engorgement was resolved in 21 (61.76%) patients. Similarly, in the control group, vascular engorgement was resolved in 9 (32.14%) patients.

Conclusions: The mean TBUT, Schirmer's score, and secretion quality score significantly increased, and lissamine green staining significantly decreased in the cyclosporine group compared to the control group. Hence, cyclosporine is one of the best choices for treating dry eye associated with meibomian gland dysfunction.

Keywords: Dry eye, Meibomian gland dysfunction, Cyclosporine 0.05%.

Introduction

Meibomian Gland Dysfunction (MGD) is an abnormality of the meibomian gland that blocks the secretion of lipids. Without sufficient lipid production, tears evaporate quickly, causing dry eye [1]. MGD results from meibomian gland orifice blockage due to plugging with solidified secretions and hyperkeratosis of the duct epithelium [2,3]. It can also be caused by atrophy or inflammation of meibomian gland acini [2,4]. Dry eye disease (DED) is a chronic ocular surface disease characterized by the instability of the tear film or an imbalance of the ocular surface microenvironment due to abnormal quality, quantity, and dynamics of tears [5]. It is accompanied by an increase in the osmolarity of the tear film as well as ocular surface irritation [6,7]. Tears are comprised of three layers. The fluid layer that nourishes the eye is known as the aqueous layer. The mucin layer contains mucus that aids in the adhesion of the aqueous layer to the eye's surface. Tears are made up of a lipid coating created by the meibomian glands in the eyelids, which serves to prevent evaporation and acts as a barrier to the environment. Meibomian gland dysfunction is an anomaly of the meibomian gland that prevents lipid release. Tears evaporate quickly if there is insufficient lipid production, resulting in dry eyes [8]. Meibomian Gland Dysfunction occurs when the ductal epithelium of the meibomian glands be-

comes hyperkeratinized, resulting in increased intraductal pressure and stoppage of normal meibum flow. Meibomian ducts obstruction leads to accumulation and thickening of lipids and colonization of bacteria on the lid margins, resulting in inflammation of the lid margins. The secondary outcome may be a defect of the tear film and related dry eye disease [8]. Increased inflammation is associated with symptoms and signs of patients [9-10]. Anti-inflammatory agents such as steroids, macrolide antibiotics, tetracycline, and cyclosporine A (CsA) have been used to treat inflammation in MGD and improve symptoms and signs of MGD [11,12,13]. The present study aimed to evaluate the clinical safety and efficacy of 0.05% cyclosporine nano-emulsion in treating dry eye syndrome associated with meibomian gland dysfunction at a tertiary care center in Muzaffarpur, Bihar, India.

Material & Methods

The present study was conducted in the Department of Ophthalmology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, from September 2023 to January 2024. Data were collected irrespective of age and sex using the OSDI questionnaire (Ocular Surface Disease Index). The OSDI questionnaire is a 12-item survey that quickly assesses symptoms of ocular irritation in dry eye and their influence on vision-related functions. Patients who visited the Ophthalmic OPD with eye problems were selected for the study. Complete ophthalmic examinations were performed on all patients.

Inclusion Criteria:

1. Age > 18 years

2. Presence of conjunctival hyperemia (tarsal and bulbar), lid margin (inflammation) vascular engorgement or thickening or irregularity of eyelid margins, and meibomian gland orifice inclusion (plugging)

3. Score > 12 on the OSDI questionnaire

Exclusion Criteria:

Patients were excluded from the study if they had a history of contact lens use (unless discontinued for at least 30 days), any infectious disease excluding blepharitis, history of glaucoma, undergone any ocular surgery within the past 3 months, active ocular allergies, treatment with isotretinoin within the past 6 months, autoimmune disease requiring systemic treatment, history of hypersensitivity reaction to oral cyclosporine A, pregnancy or nursing, or use of oral contraceptives.

Methods:

Patients who were diagnosed with dry eyes due to meibomian gland dysfunction were invited to take part in the study. Patients fulfilling the inclusion criteria were enrolled, resulting in a total of 80 participants. These patients were categorized into two groups: the experimental group and the control group, with 40 patients in each group.

All patients were advised on lid hygiene and lid warming massage for 10 minutes before sleep. Additionally, they were instructed to instill 0.1% sodium hyaluronate eye drops (preservative-free) four times a day. Patients in the experimental group were also advised to use topical 0.05% cyclosporine eye drops twice a day. The control group received only 0.1% sodium hyaluronate eye drops and did not use cyclosporine eye drops.

Tear volume assessment was conducted using the Schirmer's test without topical anesthesia, employing Whatman filter paper 41 to measure reflex secretion. The normal range for tear volume is greater than 10 mm in 5 minutes.

Tear film stability was assessed using tear film breakup time (TBUT): a method that measures the stability of the pre-ocular tear film. This was achieved by placing a moistened fluorescein strip on the eye, and using a slit lamp to observe the time between the last blink and the appearance of the first dry patch. A TBUT average of higher than 10 seconds is considered normal.

Tear film composition was evaluated through tear osmolarity measurements. Corneal evaluation was conducted using fluorescein staining, while lissamine green staining was utilized for conjunctival assessment. The severity of staining was graded according to the Oxford grading scale (mild, moderate, and severe).

Lid evaluation involved using a slit lamp to examine lid morphology, assess the expression of meibomian glands, and determine blink rate. Tear film stability was assessed using tear film breakup time (TBUT), a method that measures the stability of the pre-ocular tear film. This was achieved by placing a moistened fluorescein strip on the eye, and using a slit lamp to observe the time between the last blink and the appearance of the first dry patch. A TBUT average of higher than 10 seconds is considered normal.

Tear film composition was evaluated through tear osmolarity measurements. Corneal evaluation was conducted using fluorescein staining, while lissamine green staining was utilized for conjunctival assessment. The severity of staining was graded according to the Oxford grading scale (mild, moderate, and severe).

Lid evaluation involved using a slit lamp to examine lid morphology, assess the expression of meibomian glands, and determine blink rate.

Grading scale for meibomian gland secretion and expression: (6)

1. Clear - Normal

2. Cloudy - Turbid

3. Granular - Turbid with particulate matter

4. Inspissated - Toothpaste-like

All patients were evaluated at their first visit and followed up after 3 months of treatment to determine the therapeutic effect.

Statistical Analysis: Data was analyzed with the help of SPSS software. All data was tabulated. Percentages and Mean ± Standard deviations were observed. P- value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Results:

In our study, a total of 80 subjects were included; 40 subjects were in the experimental group, and 40 subjects were in the control group. The mean age was 51.76 ± 17.28 years in the experimental group, whereas it was 48.96 ± 12.54 years in the control group, without any statistically significant difference ($p = 0.409$). Out of 40 cases in the experimental group, 18 (45%) were males and 22 (55%) were females, whereas in the control group, 17 (42.5%) were males and 23 (57.5%) were females. There was an improvement in OSDI scores with respect to symptom intensity, frequency, and aggravation in both groups. In single analysis, the cyclosporine A 0.05% group showed a significant improvement for each score at 3 months ($p<0.001$, $p = 0.001$, $p = 0.01$, respectively).

Table 1: Gender wise distribution.

Gender	Cyclosporine group	Control group
Male	18(45%)	17(42.5%)
Female	22(55%)	23(57.5%)
Total	40(100%)	40(100%)

Table 2: Showing mean TBUT

	Cyclosporine group				Control group			
	Pre treatment	Post treatment	Mean difference	p-value	Pre treatment	Post treatment	Mean difference	p-value
Mean TBUT	7.42±2.76	13.31±4.12	5.91	<0.0001	9.56±3.24	12.65±2.87	3.15	<0.0001

When we compared the mean pre-treatment (7.42 ± 2.76 seconds) and post-treatment (13.31 ± 4.12 seconds) TBUT of cyclosporine group patients, the difference was statistically extremely significant ($p < 0.0001$). Similarly, the mean pre-treatment (9.56 ± 3.24 seconds) and post-treatment (12.65 ± 2.87 seconds) TBUT in the control group also showed statistically extremely significant differences ($p < 0.0001$). However, the greater mean difference was observed in the cyclosporine group (5.91 seconds) compared to the control group (3.15 seconds).

Table 3: Showing mean Schirmer's score

Mean Schirmer's score	First visit	Last visit (after 3 months)	Mean difference	p-value
Cyclosporine group	4.22±2.43	12.65±4.23	8.43	<0.0001
Control group	4.13±2.32	7.16±3.54	3.03	<0.0001

When we compared the mean Schirmer's score of the first visit (4.22 ± 2.43 mm) and the last visit (12.65 ± 4.23 mm) of patients in the cyclosporine group, the difference was statistically extremely significant ($p < 0.0001$). Similarly, in the control group, the mean Schirmer's score of the first visit (4.13 ± 2.32 mm) and the last visit (7.16 ± 3.54 mm) also showed a statistically extremely significant difference ($p < 0.0001$). However, the greater mean difference was observed in the cyclosporine group (8.43 mm) compared to the control group (3.03 mm).

Table 4: Showing mean of lissamine green staining

Lissamine green staining	Pre-treatment	Post-treatment (after 3 months)	Mean differences	p-value
Cyclosporine group	2.84±0.14	1.28±0.16	1.59	<0.0001
Control group	2.26±0.17	2.35±0.19	0.09	0.0284

The mean lissamine green staining score of the pre-treatment (2.84 ± 0.14) and post-treatment (1.28 ± 0.16) in the cyclosporine group showed statistically extremely significant differences ($p < 0.0001$). Similarly, in the control group, when comparing the mean lissamine green staining score of pre-treatment (2.26 ± 0.17) and post-treatment (2.35 ± 0.19), the difference was not statistically significant ($p = 0.0284$).

Table 5: Showing mean secretion quality score

Mean secretion quality score	Pre-treatment	Post-treatment (after 3 months)	Mean differences	p-value
Cyclosporine group	3.89± 0.96	1.54± 0.67	2.35	<0.0001
Control group	3.42± 0.57	3.16± 0.61	0.26	0.0729

When we compared the initial mean secretion quality score of pre-tests (3.89 ± 0.96) and post-tests (1.54 ± 0.67) in the cyclosporine group patients, the difference was extremely significant. Similarly, when we compared the mean secretion quality score of pre-tests (3.42 ± 0.57) and post-tests (3.16 ± 0.61) in the control group patients, the difference was not statistically significant (p = 0.0729). The mean differences were also greater in the cyclosporine group (2.35) compared to the control group (0.26).

Percentage of patients with improvement in vascular engorgement on the lid:

Total vascular engorgement on the lid was noted in 62 (77.5%) patients, with 34 in the study group and 28 in the control group. Out of 34 experimental group patients, vascular engorgement was resolved in 21 (61.76%) patients. Similarly, out of 28 control group patients with vascular engorgement, the condition was resolved in 9 (32.14%) patients.

Discussions

Dry eye can be defined as a multifactorial disease of the ocular surface characterized by a loss of homeostasis in the tear film. Tear hyperosmolarity, tear film instability, ocular inflammation, and neurosensory abnormalities are the major mechanisms involved in the disruption of this equilibrium, leading to discomfort and visual impairment.

In the present study, the mean age of the study group was found to be 51.76 ± 17.28 years. A similar finding was reported in a study by Henry D. Perry et al., where the mean age was observed to be 57 years in patients with mild dry eyes, 66 years in patients with moderate dry eyes, and 68 years in severe cases. The mean age of the patients was 44.2 years in a study by Jitender Phogat et al. and 47 years in a study by Tageldin M. Othman et al.

In the present study, DED was more prevalent in females than males. In a study by Ho-Yun Kim et al., involving 53 patients, 14 were male and 36 were female. The study by Jitender Phogat et al. included 18 women and 7 men. These findings are consistent with the observation that females are at a substantial risk for both DED and MGD development. This could be related to the effect of hormonal changes on meibomian gland function, as both androgen and estrogen receptors are present in the meibomian glands.

Meibomian gland dysfunction is characterized by blockages or other abnormalities of the meibomian gland orifices, resulting in inflammation and decreased lipid secretion. This leads to increased tear evaporation and tear film instability, damaging the ocular surface epithelium and causing dry eye syndrome. It is crucial to evaluate MGD in patients with DES. Several studies have reported that the chronic inflammatory state of MGD is associated with elevated levels of inflammatory cytokines in tears, such as epidermal growth factor, interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α). This elevation propagates MGD and causes inflammation on the ocular surface and eyelid margins through capillary expansion, resulting in abnormal meibomian gland secretion. Therefore, the 2011 Tear Film & Ocular Surface Society (TFOS) recommends initiating anti-inflammatory treatment for grade 3 MGD, severe telangiectasia, or occlusion of the meibomian gland orifices. Cyclosporine inhibits inflammatory cytokine production and T cell activity, acting on the conjunctiva and lacrimal glands to reduce inflammation and increase tear production. Several studies have reported that cyclosporine eye drops improve the symptoms of DES and other inflammatory diseases of the ocular surface.

In our study, the mean difference between pre-treatment and post-treatment OSDI scores was 12.4. The mean OSDI score in a study by Pinnita Prabhasawat et al. was 43.32. In a study by Jitender Phogat et al., the ocular symptoms score before treatment was 2.25 ± 0.41, which improved to 1.36 ± 0.14 after 4 weeks, 1.11 ± 0.18 after 8 weeks, and 0.6 ± 0.44 after 12 weeks, with a statistically significant difference (p=0.01).

In the present study, TBUT increased to 13.31 ± 4.512 seconds after cyclosporine treatment, with a mean difference of 3.5 seconds (p<0.0001). Research by Henry D. Perry et al. reported mean TBUTs of 1.21 seconds in mild cases of dry eyes, 0.27 seconds in moderate cases, and 0.00 seconds in severe cases. After treatment, mean TBUTs were 3.34 seconds in mild cases (P=0.015), 2.04 seconds in moderate cases (P=0.01), and 1.45 seconds in severe cases (P=0.001). Similar results were found in a study by Jitender Phogat et al., where TBUT improved from 5.49 ± 0.91 seconds before treatment to 7.91 ± 0.88 seconds after 4 weeks, 8.09 ± 0.15 seconds after 8 weeks, and 9.86 ± 0.84 seconds after 12 weeks, with a statistically significant difference (p=0.001).

In the present study, the mean lissamine green staining score in the cyclosporine group was 2.84 ±

0.14 before treatment and 1.28 ± 0.16 after 3 months (p<0.0001). In a study by Henry D. Perry et al., lissamine green staining scores at baseline were 0.29 in mild cases (range, 0-2), 0.55 in moderate cases (range, 0-2), and 2.46 in severe cases (range, 1-4). After treatment, these scores were 0.18 in mild cases (P=0.001), 0.48 in moderate cases (P=0.0078), and 1.62 in severe cases (P=0.001).

The mean Schirmer's score among patients was 4.22 ± 2.43 mm at the first visit. After 3 months, the average Schirmer's score had improved by 8.43 mm, which was statistically significant (p<0.0001). According to a study by Henry D. Perry et al., the mean Schirmer's test scores at baseline were 8.67 mm in mild cases, 6.33 mm in moderate cases, and 2.37 mm in severe cases. After therapy, the mean Schirmer's scores were 9.23 mm in mild cases (P=0.109), 7.64 mm in moderate cases (P=0.015), and 3.33 mm in severe cases (P=0.05).

In the present study, lid telangiectasia improved in 61.76% of patients. In the study by Ho-Yun Kim et al., mild lid telangiectasia was found in 38 eyes, moderate telangiectasia in 63 eyes, and severe telangiectasia in 5 eyes.

Thus, cyclosporine is a widely used anti-inflammatory agent for the management of dry eye disease. It regulates immune function in conjunctival and lacrimal cells, reducing inflammation and increasing tear production. Due to these properties, topical cyclosporine has been successfully used to treat dry eye and other ocular inflammatory diseases. Although inflammation is not the core mechanism of meibomian gland dysfunction, it induces atrophy of secretory acini and evaporative dry eye syndrome. It also increases the viscosity of meibum through changes in meibum quality and quantity. Therefore, reducing inflammation with cyclosporine appears to improve symptoms of meibomian gland dysfunction and dry eye syndrome.

Conclusions:

The mean TBUT, Schirmer's score, and secretion quality score significantly increased, and lissamine green staining significantly decreased in the cyclosporine group compared to the control group. Hence, cyclosporine is one of the best choices for treating dry eye associated with meibomian gland dysfunction.

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