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Efficacy of Topical Insulin Eye Drops In Dry Eye Disease

Samar Fatima, Muhammad Jahanzaib, Khalid Baloch, Maeirah Shafique, Fakhar Humayun, Junaid Afsar

ABSTRACT

Objective: To seesee(ASSESS/ EVALUATE)evaluate the treatment efficacy of topical insulin eye drops in patients suffering from dry eye disease (DED) by assessing improvement in corneal epithelialization, conjunctival hyperemia and corneal staining assessed before and after 3 months of therapy.

Study Design and setting: Prospective analytical study, Department of Oophthalmology, Combined Military Hospital Lahore from January-June 2025.

Methodology: A total of 390 patients with dry eye disease received topical insulin drops 1 U/ml, one drop in each eye to be taken 6 hourly for a total duration of 3 months. Primary variables studied were improvement in epithelial defects, corneal staining and hyperemia by comparing before and after 3 months of topical insulin therapy.

Results: Median hyperemia grade before therapy was 3.00 (1.00) before therapy and it was 1.00 (0.00) when assessed after treatment at 3 month follow-up ($p<0.001$). Similarly, median corneal staining grade showed median scores of 9.00 (1.00) before therapy and scores were 5.00 (2.00) at the 3 months follow-up after end of topical insulin treatment ($p<0.001$). Corneal epithelialization defect was improved by 50% in patient with mild, moderate and severe grading score before therapy.

Conclusion: We conclude that topical insulin can be recommended as an effective first line management option in patients with dry eye disease improving hyperemia, corneal staining and epithelial defects.

Key Words: Dry, disease, eye, insulin, topical

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INTRODUCTION

Dry eye disease (DED) also known as keratoconjunctivitis sicca is a disease affecting the tear film of the eye covering the epithelial surface of the cornea and the conjunctiva.[1] The tear film is a thin layer of fluid responsible for a multitude of function including lubrication, ensuring a smooth surface for refraction, preventing infection, inflammation and desiccation while ensuring oxygenation and nourishment to the eye.[2] The two main causes for DED are reduced tear film production or increased evaporation. The 2017 TFOS DEWS II report defines DED as a disease in which inflammation, hyperosmolarity, and neurosensory abnormalities play central roles in pathogenesis. Associated signs and symptoms include discomfort, itching, corneal epithelial damage, loss of visual acuity and increased frequency of infections. The reported worldwide prevalence for DED ranges from 5-50% depending upon patient age, population demographics and geographical area.[3]

DED is broadly classified into two main subtypes including aqueous-deficient dry eye, resulting from inadequate tear secretion (often due to lacrimal gland dysfunction), and evaporative dry eye, which arises from excessive tear evaporation, frequently related to meibomian gland dysfunction. These subtypes may coexist, contributing to a mixed disease presentation. The underlying pathophysiology for the disease involves a complex interaction between local hyperosmolarity, tear film instability, neurosensory abnormalities and ocular surface inflammation.[4] Clinically, DED presents with symptoms

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such as foreign body sensation, burning, stinging, fluctuating vision, and ocular fatigue. Diagnostic evaluation incorporates both subjective symptom assessment (e.g., Ocular Surface Disease Index) and objective tests such as tear breakup time (TBUT), Schirmer test, tear osmolarity measurement, and ocular surface staining with fluorescein, lissamine green, or rose bengal.

Risk factors aggravating the condition include increasing age, female gender, environmental exposures, prolonged digital device usage and autoimmune diseases. [5] Gap in literature shows that despite a high number of patients presenting with the condition, there have been no standard treatment guidelines and decision for therapy endpoints. [6] Secondly, novel non-invasive treatment options including insulin like growth factors (IGFs), autologous serum, topical fibronectin and hemoderivative products require further conclusive studies to add them to standard treatment regimens.

Topical insulin has emerged as a potential therapeutic agent in ocular surface disorders, including Dry Eye Disease (DED), particularly in cases associated with epithelial healing defects. Insulin, beyond its systemic metabolic functions, exerts trophic effects on epithelial cells, promoting proliferation, migration, and differentiation. These properties are crucial in restoring corneal epithelial integrity and tear film stability in DED. Insulin receptors are expressed on corneal and conjunctival epithelial cells.[7] Upon topical application, insulin activates the PI3K/Akt and MAPK signaling pathways, enhancing cell survival, cytoskeletal remodeling, and wound healing.[8] Additionally, insulin may modulate inflammatory responses by reducing pro-inflammatory cytokine expression (e.g., IL-1β, TNF-α), thereby attenuating the inflammatory cycle characteristic of DED. For DED, especially in diabetic patients with impaired corneal innervation and tear secretion, topical insulin has been proposed to enhance epithelial health, improve tear film quality, and reduce symptoms. Insulin in the topical form is closely associated with IGFs and is proposed to be effective in improving corneal inflammation and damage associated with DED. [9] The presence of insulin receptors in the epithelium of the cornea and presence in the tear film have advocated its use. [10]

While early results are promising, topical insulin is not yet a mainstream therapy for DED. Most studies are small-scale or focused on secondary dry eye in specific contexts (e.g., diabetic keratopathy). Long-term safety data are limited, and optimal dosage regimens remain to be standardized. The rationale of our study is to evaluate the treatment efficacy of topical insulin eye drops in patients suffering from dry eye disease (DED) to formulate treatment guidelines for patients with DED presenting in our setup.

METHODOLOGY:

This prospective analytical study was carried out at the Department of Ophthalmology, Combined Military Hospital, Lahore from January – June 2025 after approval from the ethical review board of the institute vide letter no 635/2025. Sample size was calculated keeping the confidence interval at 95%, power of test at 80% with anticipated population prevalence for dry eye disease at 50%.[11] Minimum sample size came out to be 383 patients according to WHO calculator. We included 390 patients in our final study protocol as per the inclusion criteria furnished keeping margin for lost to follow-up.

Inclusion criteria included patients of both genders, ages between 18-65 years of age presenting with dry eye disease and not responding to conventional therapies (intensive lubrication, bandage soft contact lenses etc.) taken for at least 4 weeks.

Exclusion criteria included patients with infectious etiology, keratitis of infective origin, acute chemical or thermal injury and trauma to the eye, patients on other therapies for DED, patients lost to follow-up or patients who non-consented to be included in the study.

The study method included all patients according to the inclusion criteria furnished. All patients were thoroughly counselled about the study protocol before induction in the study group. All participants agreed to and ensured regular follow-up in the OPD (outpatient department) as per the study design for monthly visits for a total duration of 3 months. After inclusion in the study protocol, patient's details including age, weight, gender, and duration of disease were recorded by a resident ophthalmology unaware of the study protocol on a proforma and submitted to the analysis team daily at the end of the OPD. Prior to starting topical insulin therapy, baseline ocular parameters were recorded in all patients. Corneal epithelial defects were assessed using fluorescein staining and slit lamp examination and repeated on follow-up visits monthly and degree of improvement in all patients was recorded till the end of the study protocol at 3 months.

All patients received topical insulin drops 1 U/ml, one drop in each eye to be taken 6 hourly for a total duration of 3 months. Patients with worsening condition of the eye after 4 weeks with no improvement were excluded from the study protocol to be shifted to alternate therapies.

Corneal staining in all patients was assessed using the NEI (National Eye Institute)/Industry workshop scale using fluorescein staining. The cornea was divided into five zones (central, superior, nasal, inferior and temporal). Each zone was graded from 0-3, 0= no staining, 1= mild (few, scattered punctate spots), 2= moderate (more numerous, large punctate spots), 3= severe (coalescent staining or epithelial defect). Final grading scores for all zones was calculated and total score out of 15 was noted at the start and end of the study period to see improvement. [12] **Hyperemia** in all patients was assessed using the Efron Grading Scale, with increasing hyperemia from 0-4, 0= Normal (no hyperemia), 1= Trace

(slight redness), 2= Mild (obvious but not severe), 3= Moderate (marked, more widespread), 4= Severe (intense, deep red). Values before and after completion of treatment at 3 months were recorded and endorsed. [13] Epithelial defect size was graded using Bron's A1–A3 area classification, which stratified corneal involvement according to the proportion of the surface affected by fluorescein staining. A1: represented mild area involvement and was defined as staining affecting less than one-third of the total corneal surface, corresponding to a small, focal epithelial defect or a limited cluster of punctate lesions. A2: denoted moderate involvement, with one-third to two-thirds of the corneal surface affected, reflecting a larger but still non-diffuse epithelial defect distributed across multiple quadrants. A3: indicated severe or extensive involvement, characterized by staining over more than two-thirds of the corneal surface and consistent with a large, near-diffuse epithelial defect involving most of the cornea.

All data collected over 3 months duration was then submitted to the final analysis team unaware of the study outcomes or the protocol to prevent bias and ensure blinding. [14]

Primary variables studied were improvement in epithelial defects, corneal staining and hyperemia by comparing before and after 3 months of topical insulin therapy. Demographic data including age, weight and gender were statistically described in terms of meanSD, frequencies, and percentages when appropriate. Normality for continuous variables was checked and was in the normal range. Values for corneal staining and hyperemia using the mentioned scales were expressed as median (IQR) and compared before and after therapy using the Mann-Whitney U test. Chi-square test and Fisher Exact was used to compare frequency variables for corneal epithelization in patients with mild, moderate and severe damage as appropriate. A p value of 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0

RESULTS:

A total of 420 patients were assessed for eligibility with 10 not meeting the inclusion criteria and 15 declining to give consent to be included in the study. 5 patients were lost to follow-up, and a total of 390 patients were analyzed in the final study protocol assessment. Mean age of patients in the study group was 47.7611.34 years and mean weight was 74.705.40 kg. Gender distribution revealed 104 (26.7%) males and 286 (73.3%) females in the study group. Mean duration of disease was 8.551.52 weeks in the study group (Table-1).

Study of primary variables showed that median hyperemia grade before therapy as assessed by the Efron scale was 3.00 (1.00) before therapy and it was 1.00 (0.00) when assessed after treatment at 3 month follow-up (p<0.001). Similarly, median corneal staining grade as assessed by the NEI scale showed median scores of 9.00 (1.00) before therapy and scores were 5.00 (2.00) at the 3 months follow-up after end of topical insulin treatment (p<0.001). Grade of corneal epithelialization defect assessed before treatment was mild in 138 (35.4%) patients, moderate in 161 (41.3%) patients and severe in 91 (23.3%) patients in the study group. After 3 months of therapy, improvement was seen in 107 (27.4%) patients in the mild defect group, 82 (21.0%) patients in the moderate defect group and 63 (16.2%) patients in the severe defect group (p<0.001) (Table-2).

DISCUSSION:

The study concluded that topical insulin can be recommended as an effective first line management option in patients with dry eye disease. At the end of therapy with topical insulin drops, patients had significant improvement in disease associated hyperemia, corneal staining and more than 60% patients had significant improvement in corneal epithelialization defect.

Figure No 1: Phases of the Study

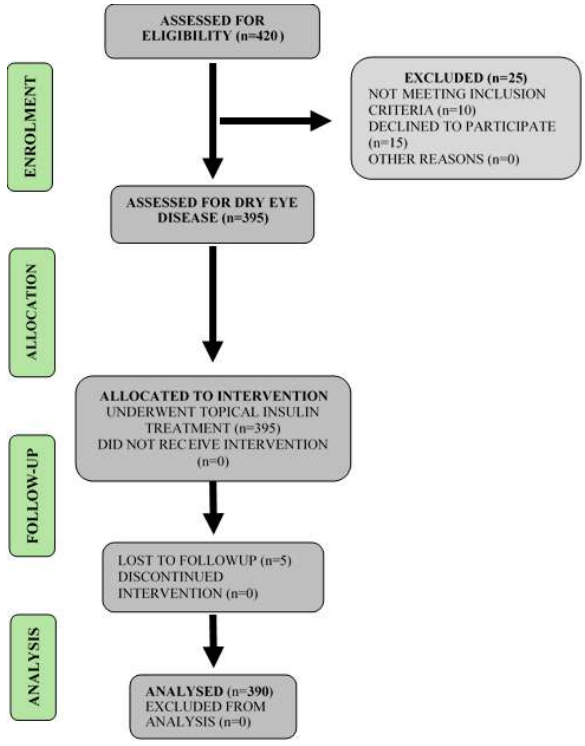

Table No 1 Demographic and Clinical Characteristics (N=390)

Variable	Topical Insulin Therapy Group (n=390)
Mean age (years)	47.76±11.34
Mean weight (kg)	74.70±5.40
Gender	
Male	104 (26.7%)
Female	286 (73.3%)
Mean duration of disease (weeks)	8.55±1.52

Table No 2 Ocular Vairables Compared Before and after Treatment (N=390)

Variable	Before therapy (n=390)	After therapy (n=390)	P value
Median Hyperemia Grade (Efron Scale) (0-4)	3.00 (1.00)	1.00 (0.00)	<0.001
Median Corneal Staining Grade (Nei Scale) (0-15)	9.00 (1.00)	5.00 (2.00)	<0.001
Frequency Of Improvement In Corneal Epithelialization Defect N (%)			
Mild	138 (35.4%)	107 (27.4%)	<0.001
Moderate	161 (41.3%)	82 (21.0%)	
Severe	91 (23.3%)	63 (16.2%)	

Comparison of our study results with local and international literature shows that in a study carried out by Burgos Blasco et al, the authors concluded accelerated corneal healing in patients receiving topical insulin drops at 1 IU/ml three times a day with observable improvements in fluorescein staining and ocular surface disease index. This is in line with results of our study with improvement in both the Efron as well the NEI scores for grading of hyperemia and corneal staining respectively.[15] In another study done by Zhang et al, the authors concluded beneficial outcome in patients with dry eye disease suffering from diabetes mellitus. They concluded that insulin in the topical form has the ability to modulate cellular metabolism and reduce ocular inflammation with improvements in corneal epithelialization defects as well as improvement in visual acuity. [16] This is in line with our study results with improvement seen both for the ocular inflammation as well as surface defect. Although not classic DED, multiple studies in epithelial defects, recurrent erosions, neurotrophic keratopathy, and post-vitrectomy diabetics consistently report faster epithelialization and good tolerance supporting the biologic plausibility for DED where epithelial stress/inflammation dominate. Case series in refractory or severe DED have demonstrated significant reductions in corneal staining and hyperemia within three months, though results may be confounded by concomitant treatments like cyclosporine or autologous serum. The therapy appears well tolerated, with negligible systemic absorption at ophthalmic doses.

In a recent systemic review and analysis, Andrade et al concluded from various randomized controlled trials and observation studies that topical insulin is very effective in improving epithelial regeneration and reduces tear film breakup time in patients with moderate to severe DED. [17] This is in confirmation of our results in which more than 50% patients in each of the mild, moderate and severe category showed a statistically significant improvement in corneal defects after the 3 months treatment period. While similar results have been reported by using autologous serum in patients with DED, a study by Krolo et al concluded that topical insulin offers easier preparation and potentially fewer immunological complications. [18]

Local studies done on the subject show that in a study carried out by Balal et al at Jinnah Postgraduate Medical Center, Karachi, topical insulin three times a day led to significant improvements in fluorescein staining and Schirmer's test scores after 6 weeks of use. One potential drawback is the lack of standard formulations for insulin in the country at present posing a challenge for widespread adoption. [19] Another local study done by Khilji et al concluded promising results in improving ocular parameters in patients suffering from neurotrophic keratopathy and diabetics suffering from dry eye disease confirming results of our study. [20]

The limitations are that the study is single center only. Long term safety profile optimized standard regimens and quality controlled delivery still remain a hurdle in widespread adoption and require further literature to recommend a broader adoption.

CONCLUSION:

We conclude that topical insulin eye drops can be recommended as an effective first line management option in patients with dry eye disease improving hyperemia, corneal staining and epithelial defects.

Conflicts of interest: Nil

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Authors Contribution:
Samar Fatima: Conception, design, analysis and interpretation of data
Muhammad Jahanzaib: Conception, design, analysis and interpretation of data
Khalid Baloch: Conception, design, analysis and interpretation of data
Maeirah Shafique: Conception, design, analysis and interpretation of data
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