ORIGINAL ARTICLE

Efficacy of Tacrolimus 0.03% Ointment in Resistant Meibomian Gland Dysfunction

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ABSTRACT

Aim: To determine the efficacy of 0.03% Tacrolimus ointment in treating resistant meibomian gland dysfunction.
Study design: Interventional case series.
Duration and Settings of the Study: From January 2021 to June 2021 at the Department of Ophthalmology, Khyber Teaching Hospital Peshawar.
Methods: Patients with meibomian gland dysfunction resistant to conventional therapy were included in the study. All of them were treated with Tacrolimus 0.03% dermatological ointment applied twice daily to eyelashes and lid margins along with lid hygiene measures. The patients were evaluated for any improvement in the subjective and objective features of the disease with therapy by conducting assessments at 2nd and 4th week of therapy and were then compared with the baseline features.
Results: A total of 18 participants (36 eyes) with mean age and ± standard deviation of 40 ± 12.4 year participated in the study. There was no statistically significant improvement in certain parameters like inferior tear meniscus level (p=0.09), meibum quality (p=0.88), conjunctival redness (p=0.18), and telangiectasia of the lower eyelid (p=0.9). However, the fluorescein staining score (p=0.03) and telangiectasia of the upper eyelid (p=0.02) showed statistically significant improvements. As far as the subjective features of the disease were concerned, significant improvement in ocular itching (p=0.04) and dryness (p=0.03) was observed.
Conclusion: Topical application of Tacrolimus 0.03% ointment showed improvement in the fluorescein staining score, telangiectasia of the upper eyelid, ocular itching and dryness in meibomian gland dysfunction in resistant cases.

Keywords: Meibomian gland dysfunction, ointment, tacrolimus.

INTRODUCTION

Meibomian gland dysfunction (MGD) is a quite common yet under-treated condition in daily ophthalmic practice. The exact pathophysiology of this condition is still not known, but it is said to be a chronic inflammatory disease of the eyelids.[17] Recently devised treatment protocols for MGD are non-curative, rather they target the ongoing inflammatory activity of the lid margins.[2-4] There are different treatment modalities like lid hygiene, omega-3 fatty acids, tree oil, artificial tears, topical/systemic antibiotics, topical steroids, and topical cyclosporine (Cs-A).[4-6] Topical steroids, either alone or in combination with antibiotic should be reserved for those who develop corneal complications such as phlyctenular keratitis or marginal keratitis. Moreover these have to be given in minimum dose enough to suppress the inflammatory activity and to prevent the development of ocular side effects like raised intraocular pressure (IOP), infective keratitis or cataract formation.[4,7,8] Those who have a suboptimal response to lid hygiene or have acne rosacea-induced blepharitis can be well treated with systemic antibiotics such as macrolides and tetracyclines.[9,10] Immune-suppressants including Topical Cs-A and Tacrolimus (TCL) are usually reserved for refractory cases of posterior blepharitis.[11,13] TCL is an immunomodulatory agent having an effect almost identical to Cs-A but with a potency of 10-100 times greater.[11,14,15] This immunomodulatory agent is extensively used in the treatment of many autoimmune diseases, in some cancer therapies, and in graft versus host diseases (GVHD).[11] TCL has recently found a space in the treatment of many inflammatory ophthalmic conditions with promising outcomes. Topical TCL has been used effectively in the treatment of atopic and vernal keratoconjunctivitis refractory to other conventional therapies, and it has been successfully used in GVHD, keratoplasties, and inflammatory cicatrizing conjunctivitis.[11,1518] There are reports of effectiveness of 0.03% topical ointment in the treatment of ocular surface inflammatory disorders and keratoconjunctivitis sicca.[12,13] The current trial determined the efficacy of 0.03% Tacrolimus ointment in treating resistant meibomian gland dysfunction, as the conventional therapies failed to resolve this condition. Furthermore, the ongoing inflammatory process leads to irreversible damage to the lid's margins.

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METHODS

This study was conducted at the Ophthalmology Department of Khyber Teaching Hospital, Peshawar from January 2021 till June 2021. Before starting the study, an ethical approval (No. 3528/R&D/IERB/ KMC) was obtained from the Institutional Ethical Review Board (IERB). The study adhered to the tenets of the Declaration of Helsinki and guidelines of good clinical practice. All the participants were informed about the objectives and significance of the study and informed consent was obtained from each participant before recruitment in the trial. A sample size of 18 (36 eyes) was calculated using the WHO sample size formula for the disease proportion prevalence. All the patients with resistant MGD were selected by non-probability convenient sampling technique from the outpatient department (OPD). The inclusion criteria consisted of those with typical features of posterior blepharitis, including tear film abnormalities, irritation, redness, swollen lids,[19,20] and previously failed conventional therapy (lid hygiene, topical/systemic antibiotics, and steroids)[21] for at least 24 weeks, and those who were willing to participate in the trial. Whereas, those were excluded who received any topical/systemic antibiotics 4 weeks before start of this study, any history of infectious eye disease or ocular procedures done within the last 24 weeks, presence of certain ocular diseases e.g., peripheral ulcerative keratitis, phlyctenular keratoconjunctivitis, leukomatous corneal scarring, corneal bullae, sterile corneal infiltrates, conjunctivochalasis, conjunctival inflammatory/autoimmune disorders or cancerous lesions. In addition, those were also excluded who had any acquired eyelid disorders (like entropion/ectropion, chalazion, or cancerous lesions), history of iridocyclitis, glaucoma, systemic drugs use that could aggravate the ocular disease entity, usage of any kind of topical medications, hypersensitivity reaction to any macrolides, contact lens use within last 3 months and pregnant women. All the participants of the trial were treated with 0.03% tacrolimus (TCL) dermatological ointment twice daily to both the eyelids in both eyes for 4 weeks along with conventional lid hygiene measures (eyelid massage, warm compresses, and lid scrubbing).For symptoms, we took ocular itching, dryness, light sensitivity, and ocular grittiness. Patients were asked to grade these complaints as 0 (None), 1 (mild) to 5 (marked). The scoring was documented in the patients' charts. Participants were assessed a day before the commencement of therapy for baseline, during 2nd week, and during the final assessment in 4th week of therapy. For ocular signs, the following tests were conducted for quantification and documentation, such as inferior tear meniscus level, tear-film break-up time (TF-BUT), fluorescein stain-pattern scoring, intensity of conjunctival redness and telangiectasia on the eyelid margins, Schirmer-I test, and meibum quality score.Inferior-tear meniscus level was measured in mm under slit lamp examination. TF-BUT and corneal staining scores were measured after applying a fluorescein strip to the lower conjunctival fornix at the outer 1/3rd (topical proparacaine 1% applied before application). TF-BUT was considered abnormal when random dots of fluorescein clearance on the cornea appeared in < 10 seconds. Corneal staining scored as 0 (None) to 8 (marked), based upon a grading system.[22] Schirmer's test was done without anesthesia, using 35mm-long Whatman No. 41 filter paper strips, folded at 5 mm on one end. This end of the paper strip was inserted into the outer 1/3rd of the inferior eyelid of the conjunctival fornix. Patients were instructed to close their eyes during the period of the test. Reading was taken after 05 minutes measuring the length of wet filter paper.Wetting of < 10mm was considered as abnormal. Meibum quality was scored from 0-3 on the meibomian glands by taking the middle-third of the upper eyelid (0 = clear, 1 = semi-solid, 2 = turbid color, 3 = hard). Conjunctival redness and superior and inferior eyelid telangiectasia were graded on a scale of 0 to 3 (0 = none, 1= mild, 2 = moderate, 3 = marked).The quantitative variables of the study (signs and symptoms) were expressed as mean and standard deviation. For statistical analysis of repeated measure variables in the study, the repeated measure ANOVA test was used for the significance of the outcome. Moreover, for analysis within the group, one paired sample t-test was used as the data was normally distributed. All analyses were performed on a software package for social sciences (SPSS) version 26.0 (IBM Corp. USA). The P-value was set at < 0.05 for the significance of all statistical tests with a confidence interval of 95%.

RESULTS

A total of 18 patients (36 eyes) with mean age and ± standard deviation of 40 ± 12.4 year were recruited in this study including 10 (55.55%) female. No statistically significant difference was found in the inferior tear-meniscus level, TF-BUT, Schirmer-I test, meibum quality, conjunctiva redness, and telangiectasia of lower eyelid when compared with the baseline (Table 1). A statistically significant difference was observed for fluorescein staining score ($p = 0.03$) and superior eyelid telangiectasia ($p= 0.02$) at 4th week. Moreover, a statistically significant difference was observed for ocular itching ($p = 0.04$) and ocular dryness ($p = 0.03$ respectively) in the 4th week and is shown in table: 2.

Table 1: Ocular Signs Assessed in Patients Treated with Tacrolimus Ointment

Ocular signs	Baseline Mean ±SD	2nd week Mean ± SD	4th week Mean ± SD	P-value
Inferior tear-meniscus level	0.39 ± 0.1	0.50 ± 0.09	0.56 ± 0.11	0.09
TF-BUT	4.11 ± 3.31	4.59 ± 3.38	5.28 ± 3.49	0.31
Fluorescein staining score	1.79 ± 1.29	0.89 ± 1.48	0.38 ± 0.69	0.03
Meibum quality	1.70 ± 0.72	1.10 ± 0.57	1.02 ± 0.7	0.88
Conjunctiva redness	1.48 ± 0.48	1.03 ± 0.79	0.80 ± 0.77	0.18
Telangiectasia UL	1.68 ± 1.09	1.38 ± 0.88	1.05 ± 0.69	0.02
Telangiectasia LL	1.58 ± 1.11	1.27 ± 1.3	0.58 ± 0.55	0.9

SD = Standard Deviation, TF-BUT: Tear-Film Break-up time, LL=Lower Lid, UL=Upper Lid
P-value is measured between the baseline occular signs and 4th Week

Table 2: Ocular symptoms assessed in patients treated with tacrolimus ointment

Symptoms	Baseline Mean ±SD	2nd week Mean ±SD	4th week Mean ±SD	P-value
Ocular itching	3.98 ± 0.9	2.04 ± 1.19	1.25 ± 1.29	0.04
Ocular dryness	3.42 ± 1.48	1.12 ± 1.32	0.55 ± 1.28	0.03
Light sensitivity	2.41 ± 2.11	1.60 ± 1.35	1.06 ± 1.2	0.88
Ocular grittiness	2.42 ± 2.3	1.71 ± 1.88	1.01 ± 1.6	0.39

SD = Standard Deviation.
P-value is measured between the baseline ocular symptoms and 4th Week

DISCUSSION

This study demonstrated the efficacy of 0.03% Tacrolimus (TCL) ointment in treating resistant meibomian gland dysfunction (MGD). A statistically significant difference found in the fluorescein staining score and upper eyelid telangiectasia revealed the effectiveness of Tacrolimus in MGD resistant to standard conventional therapies. As all the participants were refractory cases, it was assumed that they would have suffered from keratinized glandular ducts/acini with the possibility of glandular atrophic changes. With such dysfunctional alterations in the glandular tissues, we can imagine the minimal therapeutic response of topical TCL to induce its immunosuppressant effect and ameliorate the subjective features of MGD as observed in our cases. However slight improvement was observed in inferior tear-meniscus level, TF-BUT Schirmer-I test, meibum quality, and some telangiectasias of the lower eyelid but they all were statistically not significant. MGD International consensus group has explained posterior blepharitis as a condition involving the inflammation or infection of the margin of the lid at the orifices of MGs or posterior to it and the commonest etiology for it is the altered meibum obstructing the orifices of glands with all its manifestations.[21-23] The lid-flora comprises of coagulase-ve *Staphylococci, Propionibacteria, Corynebacterium, and Streptococci.* These micro-organisms are responsible for the causation of posterior blepharitis and alterations in meibum quality by producing lipases, for the production of free fatty acids and cholesterol esters that cause abnormal tear film and ocular surface damage.[2,4,6] There is an element of immune hypersensitivity in refractory cases of MGD, which is mainly due to microbial exotoxins from the lid flora or due to colonization with other strains of bacteria.TCL is converted into a pharmacologically active molecule by binding with an immunophilin. In its active form, it blocks calcineurin, which plays an important role in the signal transduction pathway by transporting the information to produce interleukins (IL-4 & 6), thus suppressing T-cells stimulation along with inhibition of B-lymphocytes via its inhibitory effects on T-Helper cells and suppressing both cell-mediated and humoral immune responses. Furthermore, TCL regulates the final stages of humoral immune system activation and thus effectively suppresses immunoglobulin synthesis.[12,13] The most reported side effects of topical TCL application were ocular irritation and stinging especially during the 1st week of its application. As its systemic absorption was minimal, no systemic adverse effects were observed in participants of our study. TCL offers a better substitute with minimal local side effects in steroid responders as well as steroid-sparing agents in steroid-induced complications. The limitations of the study included a small sample size, a short

duration of follow-up, lack of a control group, and a non-randomized clinical trial. Further prospective, randomized control blinded studies are required with a bigger sample size to further elucidate the efficacy and safety of this drug in the management of drug resistant MGD to avoid the adverse effects of prolonged steroid therapy used in such patients.

CONCLUSION

Topical application of Tacrolimus 0.03% ointment showed improvement in the fluorescein staining score, telangiectasia of the upper eyelid, ocular itching and dryness in meibomian gland dysfunction in resistant cases.

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