Effects of Topical Loteprednol Etabonate on Tear Cytokines and Clinical Outcomes in Moderate and Severe Meibomian Gland Dysfunction: Randomized Clinical Trial

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• PURPOSE: To assess tear cytokine levels and clinical outcomes in moderate and severe meibomian gland dysfunction (MGD) after 2 months of treatment with topical loteprednol etabonate and eyelid scrubs with warm compresses vs eyelid scrubs with warm compresses alone.

• DESIGN: Randomized controlled trial.

• METHODS: Patients with moderate and severe MGD were randomized into 2 groups: topical loteprednol etabonate and eyelid scrubs with warm compresses (Group I, 34 eyes) or eyelid scrubs with warm compresses (Group II, 36 eyes). We evaluated cytokine levels, tear film break-up time (TBUT), corneal and conjunctival fluorescein staining, biomicroscopic examination of lid margins and meibomian glands, and the Ocular Surface Disease Index before initiating treatment and 1 month and 2 months after treatment.

• RESULTS: There were significant decreases in the levels of interleukin (IL)-6, IL-8, and IL-1β in Group I, and IL-6 and IL-8 in Group II. Moreover, the observed decreases of these cytokines in Group I were attributed to a remarkable decrease between treatment and 1 month after treatment. In Group I, there were improvements in all of the clinical outcomes, with prominent improvement in TBUT, corneal and conjunctival fluorescein staining, and meibum quality after 1 month of treatment, compared with Group II. An improvement in meibomian gland expressibility and MGD stage reduction were more remarkable in Group I.

• CONCLUSIONS: Topical loteprednol etabonate and eyelid scrubs with warm compresses were tolerated and efficacious for the treatment of moderate and severe MGD. We suggest that such beneficial effects could manifest after 1 month. (Am J Ophthalmol 2014;158:1172–1183. © 2014 by Elsevier Inc. All rights reserved.)

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NORMAL MEIBUM LIPIDS ACT AS A BARRIER BY preventing the evaporation and contamination of the tear film and by maintaining lubrication across the ocular surface.[1] Meibomian gland dysfunction (MGD) is a prevalent condition and one of the major causes of dry eye syndrome.[2,3] MGD is a chronic, diffuse abnormality of the meibomian glands and is commonly characterized by terminal duct obstruction and changes in glandular secretion.[4] Modified and deficient meibum lipids result in tear instability, evaporative dry eye, and eyelid inflammation, which are all commonly detectable signs of MGD.[5,6]

Many investigators have reported that the chronic inflammatory status in patients with MGD is associated with high concentrations of tear cytokines.[7–10] One study compared inflammatory tear cytokine levels between MGD patients and normal controls and found that concentrations of interleukin (IL)-6 and pro-matrix metalloproteinase (MMP)-9 were significantly higher in the MGD patients.[7] Higher concentrations of IL-6, IL-8, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) were reported in dysfunctional tear syndrome with MGD.[8] Both IL-1β and IL-17 levels were elevated in tears from MGD patients.[9,10] Based on cross-sectional analysis of tear cytokine levels, a longitudinal evaluation of changes in tear cytokine levels before, during, and after treatment would be helpful in demonstrating the efficacy of treatment and in determining an effective time point for achieving treatment response.

Eyelid management, including warm compresses and lid scrubs, has been known to be a conservative and traditional treatment modality for MGD.[11] It is thought to improve meibomian gland function and ocular comfort by melting and releasing the abnormally modified meibum.[12] However, eyelid scrubs with warm compresses alone are insufficient to modulate the inflammatory process in moderate and severe MGD. Thus, eyelid management needs to be supported by additional treatment to achieve satisfactory and quick responses. Systemic tetracycline, doxycycline, and minocycline have been effective in treating moderate to severe MGD through their anti-inflammatory, antimetalloproteinase, and antiapoptotic properties.[11,13] Topical azithromycin, a macrolide antibiotic with presumed anti-inflammatory effects, has been reported to be effective for

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MGD.[14] Both topical cyclosporine and diquafosol have also shown promising results in treating MGD.[15,16]

Loteprednol etabonate, a novel C_{20} ester-based corticosteroid, was retrometabolically designed to provide potent anti-inflammatory efficacy, but with decreased impact on intraocular pressure (IOP).[17] After exerting its therapeutic effects at the site of action, it is rapidly converted to inactive metabolites, thereby resulting in fewer adverse effects.[17] Several clinical studies evaluating the efficacy of 0.5% loteprednol etabonate ophthalmic suspension (Lotemax; Bausch and Lomb Inc, Rochester, New York, USA) in patients with acute anterior uveitis, giant papillary conjunctivitis, seasonal allergic conjunctivitis, postoperative inflammation, and ocular pain showed efficacy of this medication.[18–20] In addition, many investigators reported that topical loteprednol etabonate treatment is associated with a relatively lower chance of clinically significant increases in IOP (10 mm Hg or higher).[21,22]

Based on the known efficacy and safety of topical loteprednol etabonate, we evaluated the effect of this medication in combination with eyelid scrubs with warm compresses on changes of IL-6, IL-7, IL-8, IL-1β, IL-17α, IL-12p70, monocyte chemotactic protein-1 (MCP-1), TNF-α, and IFN-γ levels and clinical outcomes in patients with moderate and severe MGD, comparing before treatment, 1 month after treatment, and 2 months after treatment. Furthermore, we compared those results with a control group treated with eyelid scrubs with warm compresses alone.

METHODS

THIS RANDOMIZED CONTROLLED TRIAL WAS APPROVED prospectively by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (Seoul, South Korea) and conducted according to the Declaration of Helsinki and Good Clinical Practices. Informed consent was obtained from all patients after explanation of the purpose and possible consequences of the study.

Inclusion criteria included patients with moderate and severe MGD.[23] MGD was diagnosed by evidence of lid margin or tarsal conjunctival erythema, bulbar conjunctival hyperemia, telangiectasia, thickening, irregularity of the eyelid margins, or meibomian gland orifice inclusions. The stage of MGD was assessed by evaluating conjunctival inflammation, clinical symptoms, fluorescein corneal and conjunctival staining, and clinical signs, including lid margin abnormality, expressibility, and altered secretion.[23] Exclusion criteria included a history of previous ocular or intraocular surgery, glaucoma or ocular hypertension, ocular infection, non–dry eye ocular inflammation, ocular allergy, autoimmune disease, history of intolerance or hypersensitivity to any component of the study medications and to other corticosteroids, wearing contact lenses during the study period, presence of current punctal occlusion, pregnancy, lactating women, and children. Additionally, patients were excluded if they were using any topical ocular or systemic medication for treatment of MGD or dry eye syndrome, including topical or oral antibiotics, topical cyclosporine A, topical or oral steroids, topical nonsteroidal anti-inflammatory drugs, topical ocular allergy medications, or artificial tears. Seventy patients who met the inclusion criteria were enrolled consecutively from the Severance Eye and ENT Hospital, Yonsei University College of Medicine, Seoul, South Korea, between August 1, 2012 and March 31, 2013. After a wash-out period of 2 weeks for patients using any other topical or systemic medication, enrolled patients were allocated randomly into 2 groups (Figure 1). A randomization sequence was created using EXCEL 2007 (Microsoft, Redmond, Washington, USA) with a 1:1 allocation using random block sizes of 2, 4, and 6, by an independent doctor. The allocation sequence was concealed from the physician enrolling and assessing patients in sequentially numbered, opaque, and sealed envelopes. After the content of the envelope was revealed, the physician and patients were aware of the allocation and the corresponding treatment. However, outcome assessors and data analysts were kept masked to the allocation. In Group I, 34 eyes of 34 patients topically received loteprednol etabonate 4 times a day following eyelid scrubs with warm compresses 2 times a day for 2 months. In Group II, 36 eyes of 36 patients received eyelid scrubs with warm compresses 2 times a day for 2 months. Four patients (4 eyes) in Group I and 6 patients (6 eyes) in Group II were lost to follow-up. Measurements of the remaining 60 eyes of 60 patients were used for statistical analysis.

The outcome assessments were performed before treatment, after 1 month of treatment, and after 2 months of treatment by 1 physician masked to group assignments. The study eye was chosen to be the eye having a higher stage of MGD. If the MGD stage for each eye was equal, the right eye was enrolled as the test eye. To minimize the extent to which 1 test influenced the results of the tests that followed, each test was performed in the same order. Tear collection was performed first, followed by the biomicroscopic examination of TBUT, corneal and conjunctival fluorescein staining, IOP measurement, examination of lid margins and meibomian glands, and the Ocular Surface Disease Index (OSDI) questionnaire. Patients were instructed to perform standard eyelid management via face-to-face education at every follow-up time and were instructed not to wipe or scrub their eyelid margins on the day of tear sampling.[11]

For tear cytokine analysis, 30 μL of phosphate-buffered saline was injected into the inferior conjunctival sac using a micropipette.[13] Approximately 20 μL of tear fluid in buffer was collected with a micropipette. In order to minimize irritation of the ocular surface or lid margin, unstimulated tear fluid was collected from the marginal tear strip of