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Topical Fluorometholone Protects the Ocular Surface of Dry Eye Patients from Desiccating Stress

A Randomized Controlled Clinical Trial

José Pinto-Fraga, MSc,[1,2] Alberto López-Miguel, PhD,[1,3] María J. González-García, PhD,[1,2] Itziar Fernández, PhD,[1,2] Alberto López-de-la-Rosa, MSc,[1] Amalia Enríquez-de-Salamanca, PhD,[1,2] Michael E. Stern, PhD,[4] Margarita Calonge, MD[1,2]

Purpose: To assess the efficacy of topical 0.1% fluorometholone in dry eye disease (DED) patients for ameliorating the worsening of the ocular surface when exposed to adverse environments.

Design: Single-center, double-masked, randomized, vehicle-controlled clinical trial.

Participants: Forty-one patients showing moderate to severe DED.

Methods: Patients randomly received 1 drop 4 times daily of either topical 0.1% fluorometholone (FML group) or topical polyvinyl alcohol (PA group) for 22 days. Corneal and conjunctival staining, conjunctival hyperemia, tear film breakup time (TBUT), tear osmolarity, and the Symptom Assessment in Dry Eye (SANDE) questionnaire scores were determined at baseline. Variables were reassessed on day 21 before and after undergoing a 2-hour controlled adverse environment exposure and again on day 22.

Main Outcomes Measures: Percentage of patients showing an increase 1 point or more in corneal staining and a reduction of 2 points or more (0−10 scale) in SANDE score, after the controlled adverse environment exposure and 24 hours later.

Results: After 21 days of treatment, the FML group showed greater improvements in corneal and conjunctival staining, hyperemia, and TBUT than the PA group ($P \leq 0.03$). After the adverse exposure, the percentage of patients having a 1-grade or more increase in corneal staining was significantly ($P = 0.03$) higher in the PA group (63.1% vs. 23.8%, respectively). Additionally, the FML group showed no significant changes in corneal staining (mean, 0.86; 95% confidence interval [CI], 0.47−1.25; vs. mean, 1.05; 95% CI, 0.59−1.51, for visit 2 and 3, respectively), conjunctival staining (mean, 0.95; 95% CI, 0.54−1.37 vs. mean, 1.19; 95% CI, 0.75−1.63), and hyperemia (mean, 0.71; 95% CI, 0.41−1.02 vs. 1.14; 95% CI, 0.71−1.58) after the exposure, whereas for the PA group, there was significant worsening ($P \leq 0.009$) in these variables (corneal staining: mean, 1.95; 95% CI, 1.57−2.33 vs. mean, 2.58; 95% CI, 2.17−2.98; conjunctival staining: mean, 1.68; 95% CI, 1.29−2.08 vs. mean, 2.47; 95% CI, 2.07−2.88; hyperemia: mean, 1.95; 95% CI, 1.63−2.26 vs. mean, 2.84; 95% CI, 2.62−3.07).

Conclusions: Three-week topical 0.1% fluorometholone therapy is effective not only in reducing ocular surface signs in DED patients, but also especially in preventing exacerbation caused by exposure to a desiccating stress. *Ophthalmology 2015;■:1−13 © 2015 by the American Academy of Ophthalmology.*

Dry eye disease (DED) is one of most common disorders in the adult population for which eye care is sought.[1] It has been reported to affect between 5.5%[2] and 33.7%[3] of the population, depending on the criteria used for DED diagnosis. Moreover, the prevalence increases with age, and currently the percentage of elderly people in the population is increasing. Another important factor contributing to the increased prevalence of DED, and certainly making it a worse problem, is the growing proportion of the population that is exposed to so-called adverse environments or desiccating stress conditions. We are currently staying longer within artificially created environments such as office buildings, shopping malls, air-conditioned vehicles, and even households. These environments are characterized by low humidity, high temperatures, and draftiness, all conditions that cause tear film alterations that usually worsen DED.[4] For many DED patients, these conditions are unbearable.[4] In addition, the number of users of visual display terminals (including tablets and smart phones) and the amount of time spent using them also have increased dramatically. These information technology devices reduce blink rate, causing tear film evaporation that can worsen DED signs and symptoms further.[5]

Currently, DED management includes the use of tear substitutes (i.e., artificial tears, lubricants, ointments),

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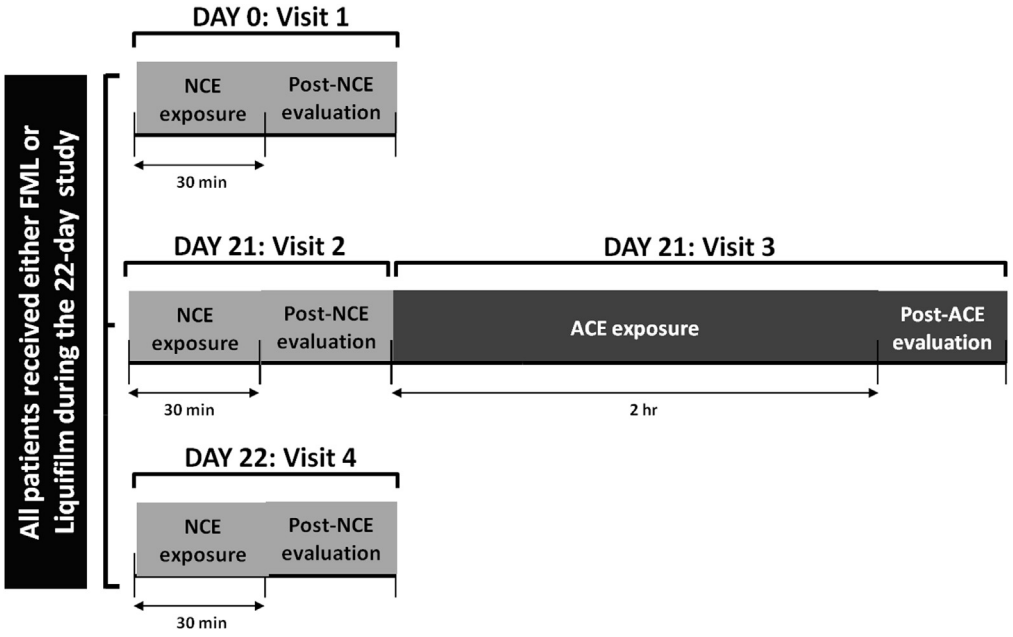

ENVIRONMENTAL CONDITION	RELATIVE HUMIDITY	T	LOCALIZED AIRFLOW
Normal Controlled Environment (NCE)	50%	23°C	NO
Adverse Controlled Environment (ACE)	5%	23°C	0.43 m/s

Figure 1. Clinical trial flowchart. ACE = adverse controlled environment; FML group = topical 0.1% fluorometholone ophthalmic suspension group; NCE = normal controlled environment; T = temperature.

punctual plugs, autologous serum derivatives, and anti-inflammatory therapy (i.e., topical cyclosporine, oral tetracyclines, and topical steroids). It also includes environmental strategies (i.e., avoiding desiccating environments and visual display terminal use) or even surgery, depending on the DED severity level.[6] Even at severity level 2, anti-inflammatory therapy is indicated,[6] including topical steroids that have been shown to be effective in several studies[7–15] and clinical trials.[16–21] However, to our knowledge, there are no reports addressing the possible protective effect of topical fluorometholone in DED patients when they are exposed to the adverse desiccating environmental conditions so often encountered in their daily life activities.[4] These conditions worsen the so-called lacrimal functional unit,[22] showing ocular surface alteration and increasing the inflammatory activity as measured in tears.[23–25]

Consequently, the main goal of the present clinical trial was not only to assess the clinical efficacy of a 3-week 0.1% fluorometholone therapy in DED patients, but more importantly, to determine if this therapy could ameliorate the expected worsening of the ocular surface after exposure to a desiccating stress set in a controlled environmental laboratory. If successful, this therapy could be of use in helping patients cope with these adverse environments. As an additional consequence, the design of this clinical trial could be helpful to ascertain if future therapies in DED also can prevent damage from desiccating stress.

Methods

This study was a single randomized, double-masked, vehicle-controlled, parallel-group, phase 3 clinical trial to explore the safety and efficacy of topical fluorometholone as a therapy for DED exacerbation provoked by exposure to an adverse controlled environment (desiccating stress) in patients with moderate to severe DED. This clinical trial was approved by the University Hospital Ethics Committee (Valladolid, Spain) and by the Spanish Regulatory Agency (Spanish Drugs and Health Products Administration; www.aemps.gob.es/en/home.htm) with EUDRA (European Union Drug Regulating Authorities) number 2013-002183-63. Moreover, the study was registered at clinicaltrials.gov (identifier, NCT02051023). The study was sponsored by and conducted at Instituto Universitario de Oftalmobiología Aplicada, University of Valladolid, Valladolid, Spain, in accordance with the tenets of the Declaration of Helsinki and in compliance with good clinical practices.

Study Procedure

The study consisted of 4 visits by DED patients over a 22-day period (Fig 1). All visits were performed in an environmental chamber within the Controlled Environmental Research Laboratory (Instituto Universitario de Oftalmobiología Aplicada, Valladolid, Spain) to control the exposure conditions carefully. More detailed information about the characteristics of this environmental chamber has been published.[25] Two different environmental conditions were used (Fig 1). The first 30 minutes of visits 1, 2, and 4 were within a normal controlled environment maintained at 23° C, 50% relative humidity, and