REDOUCTION OF CORNEAL PERMEABILITY IN PATIENTS TREATED WITH HP-GUAR: A FLUOROPHOTOMETRIC STUDY

REDDUCCIÓN DE LA PERMEABILIDAD CORNEAL EN PACIENTES TRATADOS CON HP-GUAR: ESTUDIO FLUOROFOTOMÉTRICO

ABSTRACT

Introduction: The incidence of dry eye disease, which mainly affects the corneal epithelium, is rising. The main treatment is still the use of artificial tears capable of improving the humidification and lubrication of the corneal epithelium, and avoiding its progressive functional failure. HP-Guar is a new compound used for this purpose.

Methods: We performed a prospective, masked and paired study on the left eye of 10 patients suffering from dry eye disease. Corneal permeability measurements were performed by fluorophotometry after instilling 40 µL of a solution of 2% sodium fluorescein, before and after treatment with the HP-Guar drops. The results were analysed using Wilcoxon test for paired data.

Results: A mean decrease in corneal permeability of 45%, after the use of HP-Guar drops was found (p=0.002).

RESUMEN

Introducción: El ojo seco es una enfermedad en la que entre otras estructuras se afecta el epitelio corneal. El tratamiento de primera línea siguen siendo los sustitutivos lagrimales que buscan lograr una buena humidificación y lubricación del epitelio corneal de estos pacientes, evitando así su progresivo deterioro funcional. El HP-Guar es un compuesto novedoso cuyos resultados sintomáticos en los pacientes con ojo seco están siendo prometedores.

Métodos: Presentamos un estudio prospectivo, enmascarado, pareado sobre 10 ojos izquierdos de 10 pacientes con ojo seco, a los que se les realizó medición de la permeabilidad corneal mediante fluorofotometría con la instilación de 40 microlitros de una solución de fluoresceína sódica al 2%, antes y después del tratamiento con HP-Guar. Se analizaron los resultados con el test de Wilcoxon para datos pareados.

Received: 15/2/06. Accepted: 14/6/06.
1 Graduate in Medicine.
2 Ph.D. in Medicine.
The authors declare that they do not have any commercial interest in HP-Guar or any of the products, techniques or equipment utilized in this study, in accordance with the editorial standards of Archivos.

Correspondence:
Ignacio Cerván López
Hospital Universitario Clínico San Carlos
Pabellón 8, 5ª planta
28003 Madrid
Spain
E-mail: icervan@yahoo.com
**INTRODUCTION**

Dry eye, or *keratoconjunctivitis sicca*, is defined as «a disorder of the lacrimal film due to a lacrimal deficiency or excessive evaporation which alters the inter-palpebral eye surface, associated to symptoms of discomfort» (1). The prevalence of dry eye in the adult population is estimated between 10-20% (2).

The cornea fulfills several functions: refraction, O₂ and nutrients exchange surface, support for sustaining the lacrimal film. In addition, it constitutes the first physical barrier of the eye, due mainly to its outermost layer, a non-keratinized epithelium which is stratified and squamous. On its own, the corneal epithelium accounts for over 50% of the barrier function in a healthy cornea. The union of these cells is of the «zonula occludens» type in the apical extremes and desmosomes or hemidesmosomes in the rest. These unions afford liposoluble substances very little (if any) chance of accessing the stroma and prevent the entry of polarized substances such as water or ions. Anything altering these unions would entail the loss of this barrier function.

The lacrimal film is a highly specialized and organized layer which covers, among other areas, the corneal epithelium. Alterations of the lacrimal film which involve its composition or volume can become in the short term a serious alteration of the eye surface. The ocular surface should be considered as a functional unit made up by the conjunctiva, the cornea, the eyelids, the lacrimal glands and the innervation of all these elements. A disease or dysfunction of any element of this unit leads to an unstable lacrimal film (3-6). This translates into an epithelial functional damage involving the cell unions, which leads to a rupture of the imperviousness of the epithelial barrier. In advanced cases, this leads to a keratopathy known as *keratoconjunctivitis sicca*.

Fluorophotometry is the only objective technique to assess *in vivo* the function of the epithelial barrier, utilizing fluorescein as tracer (7). Even small lesions of the corneal surface undetectable with a slit lamp ophthalmological exploration can cause a rupture of the epithelial barrier, which can be determined only via fluorophotometry (7-11).

The usual treatment for dry eye is tear substitutes which humidify the eye surface. HP Guar (hydroxypropyl guar) is a novel compound in the dry eye treatment having properties (12,13) which not only allow for humidification but also lubrication and repair of epithelial lesions.

The objective of this study is to make a fluorophotometric assessment of the role of HP-Guar in the treatment of dry eye patients.

**SUBJECTS, MATERIAL AND METHOD**

The study was prospective, masked, paired, with ten dry eye patients. Ten eyes were examined, one per patient. To avoid the selection of two eyes per subject, it was decided to study in all cases the left eye after random selection in the first patient. All patients were women with an average age of 60.3 years (SD: 3.4 years).

The inclusion criteria were: Schirmer test Type 1, under 10 mm (14) and dry eye symptoms: feeling of having a foreign body in the eye, feeling of «needles», irritation or intermittent cloudy vision.

The exclusion criteria were: wearing contact lenses, previous ophthalmological surgery or systemic disease which could alter the eye surface.

The patients left their previous treatment with artificial tears in that eye one week prior to the study.

**Conclusions:** HP-Guar provides a new therapeutic option significantly decreasing corneal epithelial permeability (*Arch Soc Exp Ofalmol 2006: 81: 327-332*).

**Key words:** Fluorophotometry, HP-Guar, dry eye, epithelial permeability, artificial tears.

**Resultados:** Se observó tuvo una disminución estadísticamente significativa de la permeabilidad corneal media del 45% tras tratamiento con HP-Guar (p= 0.002).

**Conclusiones:** El HP-Guar constituye una nueva opción terapéutica que ha demostrado fluorofotométricamente reducir la permeabilidad epitelial corneal tras su uso.

**Palabras clave:** Fluorofotometría, HP-Guar, ojo seco, permeabilidad epitelial, lagrimas artificiales.
A fluorophotometric study was made on all patients before and after the treatment with HP-Guar. The device for the analysis was the Fluorotron Master (Ocumetrics, California, EEUU).

In each visit, three measures of corneal autofluorescein were taken first, averaging the three readings. Subsequently, 40 microliters of a sterile 2% sodium fluorescein solution were instilled in the sac fundus, and waited 45 minutes before taking the following three measurements and their corresponding averages. After the pre-treatment study, we prescribed HP-Guar eye drops (Systane®, Alcon, Spain), 4 installations per day for one month. The corneal permeability (P) or condition of the epithelial barrier was of $P_{45^-} - P_{0^-}$, where $P_{45^-}$ is the mean stromal fluorescence value 45 minutes after the fluorescein instillation, and $P_{0^-}$ is the stromal fluorescence or autofluorescence before the instillation (10,11).

Before and after the treatment, patients were assessed using a slit lamp. They were rated from 1 to 3 according to the triple Madrid dry eye Classification (15): 1= slight (symptoms without signs); 2= moderate (symptoms with reversible signs); 3= (symptoms with irreversible signs). A p<0.05 was considered significant. The results were analyzed applying the Wilcoxon test for paired data.

RESULTS

The values were grouped in two categories: pre HP-Guar and post HP-Guar. The results are shown in table I.

The mean P values pre HP-Guar with a confidence interval (CI) of 95% was of 1,228.18 ng/ml and post-treatment was 629.81 ng/ml. The mean pre HP-Guar (CI 95%) was of 747.60 ng/ml, and post-treatment of 332.95 ng/ml. The mean deviation pre-treatment was 1,244.23 ng/ml, and post-treatment of 757.85 ng/ml.

As figure 1 shows, the larger the pre HP-Guar permeability the greater the reduction thereof with the treatment. The mean permeability reduction percentage was 45.96%. A statistically significant difference of p=0.002 was obtained, with an improvement in the barrier function after the treatment.

Prior to the treatment, the patients were classified as moderate dry eye (7 patients) and slight (3 patients). Of the moderate group, 4 exhibited dotted corneal tinctures over half the corneal epithelium and the remaining 3 only minimum alterations at an inferior level. After the treatment, 7 of the 10 patients stated they noticed a clear subjective improvement in the foreign body feeling, of pricking, itching and intermittent cloudy vision, with complete absence in none. All the patients reduced treatment of 332.95 ng/ml. The mean deviation pre-treatment was 1,244.23 ng/ml, and post-treatment of 757.85 ng/ml.

As figure 1 shows, the larger the pre HP-Guar permeability the greater the reduction thereof with the treatment. The mean permeability reduction percentage was 45.96%. A statistically significant difference of p=0.002 was obtained, with an improvement in the barrier function after the treatment.

Prior to the treatment, the patients were classified as moderate dry eye (7 patients) and slight (3 patients). Of the moderate group, 4 exhibited dotted corneal tinctures over half the corneal epithelium and the remaining 3 only minimum alterations at an inferior level. After the treatment, 7 of the 10 patients stated they noticed a clear subjective improvement in the foreign body feeling, of pricking, itching and intermittent cloudy vision, with complete absence in none. All the patients reduced

Table I. Results for the mean fluorophotometric permeability (P) of the sample

<table>
<thead>
<tr>
<th>Patient</th>
<th>P Pre HP-Guar (ng/ml)</th>
<th>P Post HP-Guar (ng/ml)</th>
<th>Permeability reduction in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>452.7</td>
<td>208.9</td>
<td>53.85</td>
</tr>
<tr>
<td>2</td>
<td>2743.2</td>
<td>1873.2</td>
<td>31.71</td>
</tr>
<tr>
<td>3</td>
<td>190.1</td>
<td>57.6</td>
<td>69.70</td>
</tr>
<tr>
<td>4</td>
<td>1048.3</td>
<td>425.9</td>
<td>59.37</td>
</tr>
<tr>
<td>5</td>
<td>233.1</td>
<td>201.3</td>
<td>13.64</td>
</tr>
<tr>
<td>6</td>
<td>1042.5</td>
<td>602.1</td>
<td>42.24</td>
</tr>
<tr>
<td>7</td>
<td>3375.2</td>
<td>2176.8</td>
<td>35.50</td>
</tr>
<tr>
<td>8</td>
<td>119.8</td>
<td>71.5</td>
<td>40.32</td>
</tr>
<tr>
<td>9</td>
<td>340.3</td>
<td>240</td>
<td>29.47</td>
</tr>
<tr>
<td>10</td>
<td>2736.6</td>
<td>440.8</td>
<td>83.89</td>
</tr>
</tbody>
</table>

P: permeability.
the degree of corneal tincture except one, who did refer improvement in the symptoms. In summary, a clear subjective improvement was appreciated in all the symptomatic parameters analyzed, and slight improvement in the corneal tincture in general.

DISCUSSION

The corneal epithelium barrier constitutes the most important barrier at the corneal level. Its health depends, among other factors, on a good lacrimal lubrication, without which a healthy epithelium tends to flake and erode.

There are several techniques for studying the corneal epithelium: mirror and confocal microscopy, electronic microscopy, cell cultures, electric and physiological measures, Scheimpflug images, proton MRI and fluorophotometry.

If the corneal exploration reveals dry keratopathy, it will also appear in the fluorophotometric analysis (16); but if the clinical exploration is normal, there may be a subclinical alteration of the epithelium barrier which can only be determined with fluorophotometry because this technique is the only objective one for assessing the barrier function of the corneal epithelium. Fluorophotometry has been utilized to studying the permeability of the epithelium in multiple circumstances: autofluorescence (17,18), in contact lens users (19-21), in topical treatments with and without preservatives (22-29), after surgery, in dry eye patients with diverse etiology (30,31), in systemic pathologies (32-35) and for corneal physiology studies (36-41). In a previous study we carried out, it was seen that the corneal epithelium permeability value in normal subjects is of 34.4±23.5 ng/ml (27). Thus, we see how the dry eye patients of this study have a much higher permeability than normal subjects.

Fluorophotometric studies have been carried out on other types of artificial tears (37) and their preservatives, while this is the first study being made on HP-Guar. Polyvinyl alcohol has proved its capacity to reduce permeability up to 44%, a similar amount as the results we obtained, possibly due to its mucimimetic action (38,39).

HP-Guar (Systane, Alcon, Spain) is a new active principle which has demonstrated its ability to reduce symptoms and signs of dry eye throughout the day in comparison with carboxymethylcellulose which reduces the foreign body feeling and lessens the dry feeling). HP-Guar exhibits mucimimetic activity, protects the corneal epithelium for a longer period and enhances its barrier function by facilitating epithelial regeneration (9,40). This principle is accompanied by polyethylene glycol 400 (PEG 400) and propylene glycol, and we must consider the three together as the «active principle» of the product.

Preservatives are substances which protect ophtalmological preparations against contamination and growth of pathogenic micro-organisms. Currently utilized preservatives are active against the bacterial cell membrane, damaging or destroying it. All preservatives with sufficient efficiency against micro-organisms exhibit toxic effects and a variety of allergic reactions. The patients who make frequent use of eye drops, such as dry eye patients, are more exposed to said adverse effects. The great storage capacity of the cornea and the conjunctiva facilitates toxic reactions of preservatives. Even in low concentrations, these substances reduce considerably the corneal epithelium resistance. The most widely utilized preservatives are benzalconium chloride, chlorhexidine, cetrimide, chlorine-butanol, thimerosal, polyquad ammonium chloride and biguanides. Of all these, the most toxic seems to be benzalconium chloride (41-43). The main preservative of HP-Guar is polyquad. In an in vitro study on culture of human corneal epithelium cells carried out by Tripathi et al, Polyquad exhibited no distinguishable effects on mitotic activity or on cytokinetic movements of epithelial cells (43). Accordingly, even if only the formulation of HP-Guar comprises preservative, its mucimimetic effect (9) counteracts the low toxicity of polyquad.

This is the first study to assess the effect of HP-Guar on the performance of the epithelium barrier, measured with fluorophotometry. The broad ranges of values of the mean and average of our results are because our sample includes patients with varying degrees of previous spotted epithelium lesions. The results, both for permeability reduction and alleviation of symptoms, leads us to assess HP-Guar as an efficient, toxicity-free treatment for the corneal epithelium. Even though our study comprises a small sample, the results are encouraging and it would be interesting to carry out a further study with a larger sample assessing also the results of HP-Guar without preservatives in patients with varying degrees of dry eye.

In conclusion, treatment with HP-Guar objectively improves the rupture of the epithelial barrier. It also reduces dry eye symptoms.
REFERENCES


