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Effects of topical acne treatment on the ocular surface in patients with acne vulgaris☆

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ABSTRACT

Purpose: To assess the ocular side effects during topical retinoid-antibiotic combination treatment in patients with facial acne vulgaris.
Methods: Forty-three patients applying topical isotretinoin + erythromycin combination (isotrexin gel, GlaxoSmithKline) once daily for the treatment of acne vulgaris were enrolled. Full ophthalmologic examination, Schirmer test (with topical anesthesia), fluorescein break-up time (BUT), corneal fluorescein staining and tear osmolarity measurement with the TearLab system (TearLab Corporation) were carried out before and at the end of the first month of the treatment. For evaluation of symptoms participants completed the ocular surface disease index (OSDI) questionnaire at each visit.
Results: The mean age of the patients was 23.16 ± 3.03 (18–30) years. Mean tear osmolarity increased significantly from 282.09 ± 8.95 mOsm/L at baseline to 300.39 ± 16.65 mOsm/L after the treatment ($p < 0.001$). BUT decreased from an average of 11.93 ± 1.12 s at baseline to 6.65 ± 3.03 s at the end of the first month ($p < 0.001$). The OSDI score worsened significantly (5.41 ± 3.65 vs 21.53 ± 12.95, $p < 0.001$) and punctate epitheliopathy was seen in 51% of eyes after the treatment. The average Schirmer values were 13.09 ± 1.90 and 12.41 ± 2.44 mm/5 min before and at the end of the first month of the treatment, respectively ($p = 0.117$).
Conclusions: The findings of this study indicate that topical retinoid-antibiotic combination treatment causes significant signs and symptoms of dry eye. Patients receiving topical treatment for acne should be evaluated regularly to ensure the timely detection and treatment of pathologic signs on the ocular surface.

1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit resulting from several interacting pathophysiologic factors [1]. Among these, sebaceous gland hyperplasia with hyperseborrhea, abnormal keratinization with subsequent blockage of pilosebaceous ducts, bacterial colonisation of hair follicles by Propionibacterium acnes and inflammation are the most notable factors that contribute to acne development [2].

The available topical and systemic treatment options (medical treatment, lasers, light therapy) aim to interrupt the formation of the non-inflammatory lesions, inflammation, bacterial colonization and prevent complications including acne scars. Medical treatment regimens with these targets are composed of retinoids and antibiotics. Retinoids are important tools in the management of acne because they act against all major etiologic factors implicated in acne including abnormal keratinisation, the microcomedones (the earliest clinical lesions evolving into either non-inflammatory comedones or inflammatory papules and pustules) and are also antiinflammatory [2–4]. Besides this, antibiotics are known to be the most effective therapy for inflammatory type of acne but due to potential for bacterial resistance, side effects and to increase efficacy usually combined therapy with retinoids is recommended [5].

However, it is certain that some acne vulgaris patients stop using systemic and/or topical treatment regimens because of the side effects and due to teratogenicity, caution is advised during systemic and even topical use of isotretinoin in women of childbearing age [6,7]. The most common adverse reactions observed during systemic acne treatment are mucocutaneous and ophthalmological [8]. Ocular side effects associated with systemic acne treatment particularly with oral isotretinoin usage

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were investigated many times. These undesired ocular side effects include dry eye, blepharoconjunctivitis, corneal opacities, abnormal meibomian gland secretion, conjunctival epitheliopathy, photophobia, and teratogenic ocular abnormalities [6–10].

Despite ocular adverse reactions associated with systemic acne treatment having been evaluated in detail, to our knowledge there is no study evaluating the effects of topical acne treatment on the ocular surface. This study was carried out to investigate possible side effects of a common topical retinoid-antibiotic combination (isotrexin gel, GlaxoSmithKline) on the ocular surface and to assess patient symptoms with this treatment.

2. Materials and methods

This prospective study comprised young subjects (aged 18–30 years) who applied to dermatology out-patient department of our university hospital with facial acne vulgaris. Patients with a diagnosis of mild to moderate acne, defined as those having ≥2 and ≤30 inflammatory and/or noninflammatory lesions with an Investigator's Global Assessment score of 2 or 3 were included after receiving thorough information about the study aim and procedure and providing their written informed consent.

The study was approved by the local ethical committee and was performed in accordance with the ethical principles described in the Declaration of Helsinki.

Patients were excluded if they had nodulocystic lesions, secondary acne (e.g., chloracne, drug-induced acne), pathological findings in biomicroscopical examination (e.g., eyelid margin crusting, eyelid margin thickening, eyelid margin erythema, conjunctival injection, conjunctival chemosis, filaments on the cornea, corneal scar), history of refractive surgery, ocular or systemic disease other than acne, or had hypersensitivity or a previous allergic reaction to any of the components of the study drug. Pregnancy was also an exclusion criterion.

Patients in the study applied topical isotretinoin 0.05% + erythromycin 2% combination (isotrexin gel, GlaxoSmithKline) once daily for the treatment of their facial acne vulgaris. To minimize the potential risk for overdose subjects were instructed to apply the assigned study drug using a sufficient quantity (recommended volume: 2 finger-tip units per application) to cover the entire face [11].

Full ophthalmologic examination, Schirmer test (with topical anesthesia), fluorescein break-up time (BUT), corneal fluorescein staining and tear osmolarity measurement with the TearLab system (TearLab Corporation) were carried out before and at the end of the first month of the treatment. BUT was measured using a sterile fluorescein paper diluted with a nonpreserved, balanced salt solution. While the patients were looking upward, the fluorescein paper was touched to the inferior fornix conjunctiva, and the patients were directed to blink three times. Then the patients look straight forward without blinking. The tear film was observed under cobalt blue filtered light of the slit-lamp biomicroscope, the time elapsed between the last blink and appearence of first break in the tear film was recorded. Also, slit-lamp examination of conjunctiva and cornea (which were now stained by fluorescein) using cobalt blue light was performed to look for signs of dry eye.

To perform Schirmer test and measure the basal tear secretion, a drop of topical anesthetic agent (0.5% proparacaine hydrochloride) was instilled to the inferior fornix and excess moisture on the eyelid margin was dried with a cotton tip applicator. A Schirmer test strip was placed at the inferotemporal conjunctival fornix after a few minutes. The amount of wetting was recorded after 5 min.

For evaluation of symptoms participants completed the ocular surface disease index (OSDI) questionnaire before and at the end of the first month of the treatment. The OSDI is a questionnaire including 12 questions, which are subdivided into three groups. The first group contains questions about the ocular symptoms of dry eye syndrome, the second about the ocular symptoms while watching television or reading a book, and the third group contains the questions about ocular symptoms induced by environmental factors.

2.1. Statistical analysis

All data were analyzed using SPSS software (version 16.0 SPSS, Inc, Chicago). The descriptive statistics were presented as mean ± standard deviation (SD). Only the results from the right eyes were used for statistical analysis. The paired samples *t*-test was used for the comparison between baseline values and the measurements performed at the end of the first month of the treatment. A *P* value less than 0.05 was considered statistically significant.

3. Results

The study comprised 43 eyes of 43 patients. The mean age of the patients was 23.16 ± 3.03 (18–30) years. Table 1 summarizes demographic characteristics of the subjects.

Mean tear osmolarity increased significantly from 282.09 ± 8.95 mOsm/L at baseline to 300.39 ± 16.65 mOsm/L after the treatment ($p < 0.001$). At the end of the first month of the treatment 13 patients (30.2%) had a tear osmolarity spike more than 305 mOsm/L cut-off value, and 11 of them (25%) also had a tear osmolarity spike more than 308 mOsm/L cut-off value for dry eye.

BUT decreased from an average of 11.93 ± 1.12 s at baseline to 6.65 ± 3.03 s at the end of the first month. The OSDI score worsened significantly (5.41 ± 3.65 vs 21.53 ± 12.95, $p < 0.001$) and punctate epitheliopathy was seen in 22 eyes (51%) after the treatment. The average Schirmer values were 12.84 ± 5.13 and 11.61 ± 4.90 mm/5 min before and at the end of the first month of the treatment, respectively (Table 2).

One patient had blepharitis and hyperemia of the lid margin at the end of the first month of the treatment.

4. Discussion

Topical therapeutic agents are commonly used as the first-line therapy for the management of mild to moderate acne vulgaris [3]. There is increased evidence supporting the recommendation of a combination of a topical retinoid plus an antimicrobial agent as first-line therapy for most patients with acne as a means of targeting multiple pathogenic features and both inflammatory and noninflammatory acne lesions [12]. Thus, knowledge of, and warning of, a common topical retinoid-antibiotic combination induced side effects is fundamental. In this study, we have demonstrated for the first time that topical antiacne treatment induces significant signs and symptoms of dry eye.

Of the ocular side effects associated with systemic isotretinoin (an ingredient of our study drug), signs and symptoms of ocular surface alterations are common and up to 30% of patients treated with this drug complain about dry eyes [13]. Animal data of histopathological changes in the eyelids caused by systemic

Table 1
Demographic characteristics of the subjects.

Age (years)	23.16 ± 3.03
Sex (female/male)	28/15
Refractive error	−0.075 ± 0.84

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