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The effect of systemic isotretinoin treatment on skin biophysical parameters among patients with acne vulgaris*

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Background/aim: Systemic isotretinoin has been widely considered an effective and safe medical treatment for severe and refractory acne for nearly 3 decades. However, it also appears to cause undesirable cutaneous side effects. The aim of this study was to prospectively measure biophysical parameters of skin function among patients with acne vulgaris before and after 3 months of isotretinoin therapy, including pH, temperature, sebum content, skin hydration, and transepidermal water loss.

Materials and methods: The study cohort consisted of 19 patients with acne vulgaris. Noninvasive methods were used to measure the biophysical characteristics of forehead skin. All measurements were repeated following the completion of 3 months of systemic isotretinoin treatment.

Results: Biophysical skin parameter measurements after 3 months of isotretinoin therapy revealed a decrease in the severity of seborrhea. However, the skin was dry, indicting a decrease in stratum corneum hydration. An increase in skin temperature was also determined.

Conclusion: Treatment with systemic isotretinoin reduces sebum secretion and stratum corneum hydration and increases skin temperature, suggesting that isotretinoin may partially improve the biophysical characteristics of the skin among patients with acne vulgaris.

Key words: Acne vulgaris, isotretinoin, retinoids, biophysical skin parameters

1. Introduction

Acne is a frequently self-limiting intermittent or chronic inflammatory condition affecting the pilosebaceous glands of the skin, most commonly occurring in adolescents. The clinical characteristics of acne include erythematous papules, comedones, pustules, and occasionally pseudocysts or nodules. A number of conventional systemic and topical treatments have been demonstrated to effectively reduce lesions. However, oral isotretinoin therapy has been shown to dramatically improve the treatment and management of refractory or severe acne. Oral isotretinoin therapy may result in extended periods of disease remission or resolution (1–4). Oral isotretinoin is effective in the treatment of acne vulgaris as a result of direct suppression of the microcomedone and sebaceous glands (5).

The skin is a multifunctional organ and the largest in the body. It absorbs ultraviolet radiation, combats microorganism invasion and chemical penetration, and regulates the passage of water and electrolytes. The skin also plays a major role in thermoregulation, in addition to performing immunological, sensory, and autonomic functions. It is essential to be aware of the physiological, chemical, and biophysical characteristics of the skin if the correct approach to the management of dermatological diseases is to be identified. However, the effects of genetic and environmental factors on the majority of cutaneous characteristics must also be considered (6).

Despite the widespread use of isotretinoin in the treatment of nodular-cystic acne and refractory acne, few studies have examined the effects of systemic isotretinoin therapy on the biophysical parameters of skin (7). This study investigated biophysical changes in the skin of patients with acne vulgaris and the effect of treatment on these changes. Skin humidity, transepidermal water loss (TEWL), sebum content, temperature, and pH were

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determined using noninvasive procedures in acne patients before and after isotretinoin therapy.

2. Materials and methods

2.1. Patients

The experimental procedures were conducted in the Dermatology Department of the Faculty of Medicine, Erciyes University, Kayseri, Turkey. The Erciyes University Medical School Ethics Committee reviewed and approved the study protocol. All study participants provided informed consent.

The subjects included 19 patients aged ≥18 years who presented to the outpatient clinic with moderate to severe acne vulgaris. None of the participating patients had benefited from previous acne treatments and they had not received any acne medication during the previous 30 days.

All patients were provided with materials informing them of the potential side effects of isotretinoin. A daily dose of 0.5–0.75 mg/kg was applied as the initial treatment. All patients were evaluated at regular intervals. Laboratory and clinical examinations were completed prior to treatment and at monthly intervals following the initiation of therapy.

All application of topical moisturizing agents and cosmetics was withdrawn for 48 h prior to experimental evaluations. Biophysical measurements of forehead skin were repeated at 3 months after the initiation of therapy.

2.2. Analytical methods

Noninvasive methods were used to determine the biophysical properties of forehead skin. This included use of a Tewameter (TM 210), Sebumeter (SM 810), Corneometer (CM 825) and pH meter (PH 900) (Courage + Khazaka Electronic GmbH, Cologne, Germany) (8–10).

Stratum corneum hydration status was calculated after measurement of electrical capacitance using the Corneometer (CM 825). The dielectric constant is dependent on the level of skin hydration, resulting in changes in tissue capacitance when the probe is pressed to the forehead at a pressure of 7.1 N/cm^2. Specific units of measurement (11–14) are equivalent to 0.02 mg/cm^2 water at 20 nm below the skin surface.

Quantitative determination of skin surface lipids, primarily corneal lipids and sebum, was completed using the Sebumeter (SM 810). This device quantifies light transmission through a sebum-coated sheet of plastic stained for lipids; the procedure is not influenced by environmental humidity. The Sebumeter is applied to the skin for 0.5 min at a constant force of 9.4 N/cm^2. The sebum concentration is quantified as μg/cm (11,12). Sebum content was measured at baseline, prior to the application of any facial wipes or cleansers.

An evaporation meter was used to determine TEWL (Tewameter TM 210). The recommendations of the European Group for Efficacy Measurements on Cosmetics and Other Topical Products were used in all cases (expressed in g m^{-2} h^{-1}) (15). The same device was used to measure skin temperature.

A pH meter was used to measure skin pH (PH 900).

The same investigator performed all measurements (EÇ). No information regarding the biophysical properties of the skin was provided to the study participants. All measurements were taken from a representative seborrheic area, the forehead.

2.3. Measurement conditions

Room temperature was set to 20–22 °C and ambient humidity was maintained at 40%–45%. Prior to measurement, patients were held in the test room for 30 min, with the measurement sites uncovered, to allow the skin to adapt to room temperature and humidity. Measurements were performed between 1400 and 1600 hours to exclude the effects of diurnal variation.

2.4. Statistical analysis

The results are reported as mean ± standard deviation. The characteristics analyzed diverged significantly from normal distribution. The nonparametric Wilcoxon paired test was therefore used to compare our findings before and after 3 months of isotretinoin therapy. $P < 0.05$ was considered statistically significant.

3. Results

The mean age and sex distributions did not differ significantly among the patients (20.47 ± 3.27 years, 9 males and 10 females).

There were no significant changes in TEWL and pH after 3 months of isotretinoin therapy. The degree of skin sebum content was reduced from the value of 257.7 ± 67.5 μg/cm^2 to 64.9 ± 63.4 μg/cm^2. The degree of stratum corneum hydration significantly decreased; its mean was 57.9 ± 17.6 mg/cm^2 prior to treatment and 46.1 ± 14.8 mg/cm^2 after 3 months of treatment. The skin temperature significantly increased from 24.3 ± 2.02 °C to 26.5 ± 2.6 °C. The mean value differences for each parameter are shown in the Table.

4. Discussion

Isotretinoin has been used as a safe and effective medication for the management of severe and refractory acne for nearly 30 years. This drug potently modulates all major factors in the pathogenesis of acne and is the only approach with the potential to produce a permanent cure or long-term remission of acne (1,2,5). Previous studies have emphasized the possibility of numerous undesirable side effects during isotretinoin treatment. Isotretinoin tolerance is reported to be highly dose-dependent. When isotretinoin is used at daily doses higher than 0.5 mg/kg, lesions of the skin and mucous membranes are observed

Table. Results of skin measurements before and after 3 months of treatment.

Measurements	Before treatment n = 19 Mean ± SD	After 3 months of treatment n = 19 Mean ± SD	P
Sebum content (Sebumeter units; μg/cm^2)	257.7 ± 67.5	64.9 ± 63.4	<0.001
TEWL (Tewameter units; g m^{-2} h^{-1})	29.6 ± 20.9	29.9 ± 13.1	0.6
pH	5.9 ± 0.7	6.2 ± 1.08	0.38
Skin capacitance (Corneometer units; 0.02 mg/cm^2)	57.9 ± 17.6	46.1 ± 14.8	0.04
Temperature (°C)	24.3 ± 2.02	26.5 ± 2.6	<0.01

in almost all patients. Previous studies reported varying degrees of cheilitis in 96% of patients, and some authors suggested that this represents an accurately selected dose (16). Other common side effects include cutaneous and mucous dryness, conjunctivitis, pruritus, and sensitivity to ultraviolet radiation, as well as sparse hair and hair thinning. Variations in basic laboratory test results, such as blood cell count, transaminases, bilirubin, blood lipids, and alkaline phosphatase levels, have been observed in some cases. This may also indicate the need to lower the dose administered or the addition to treatment of other medicaments (3,17). Our patients also reported side effects, including dry skin, burning sensations, and drying of the mucous membranes. Skin dryness in treated patients directed our attention toward the skin barrier function.

Isotretinoin treatment reduces the size and secretions of the sebaceous glands (7,18,19). Sebumeter measurements revealed a significant decrease in the degree of cutaneous sebum content, as also confirmed by previous studies (7,18,19).

Kmieć et al. (7) reported a decrease in stratum corneum hydration and an increase in TEWL values in patients with acne receiving isotretinoin therapy. We determined a significant decrease in stratum corneum hydration, but no difference in TEWL values. The absence of a difference in TEWL values may possibly be due to treatment not yet having been completed. Disruption of the epidermal barrier, resulting in a decrease in stratum corneum hydration, also causes the widespread skin discomfort described by patients.

We determined an increase in skin temperature. Kmieć et al. (7) did not assess posttreatment skin temperature, but they did report an increase in the erythema levels they measured. Thinning of the skin and increased erythema during isotretinoin therapy may be responsible for the increase in skin temperature.

Studies have reported a rise in pH following isotretinoin therapy (7). In our study, pH values after 3 months of oral isotretinoin therapy rose by a mean 0.3 units, although this increase was not statistically significant. Longer periods of systemic isotretinoin therapy in acne vulgaris may be required to significantly alter these biophysical parameters.

This study is limited by the relatively small sample size, the evaluation of skin biophysical parameters at a single skin site, and the fact that no measurements were made at the completion of therapy.

Our findings confirm that adverse cutaneous and mucous membrane reactions may be seen during isotretinoin therapy, and these were observed in the great majority of patients. Such reactions and poor tolerance of them have been reported by a number of previous studies (3,5,7,17,18). We therefore recommend that patients be given suitable skin care instructions during isotretinoin therapy. Formulations that moisturize the skin should be preferred, and care should be taken that cleaning agents do not leave the skin dry.

In conclusion, systemic isotretinoin therapy resulted in decreased sebum content, stratum corneum hydration, and increased skin temperature after 3 months, but no change was observed in the other biophysical parameters measured. These results suggest that systemic isotretinoin may improve the biophysical characteristics of the skin through both direct and indirect mechanisms. Further long-term and large-scale studies evaluating the effects of acne vulgaris treatment on both functional and histomorphological changes may be required to fully characterize the effects of systemic isotretinoin on skin physiology.

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