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Lowering lesional surface pH in acne: A new treatment modality for Herpifix®

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THERAPY

Lowering lesional surface pH in acne: A new treatment modality for Herpifix®

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Abstract

The acid skin surface pH has antimicrobial activities. Increased growth of *Propionibacterium acnes* contributes to the pathogenesis of acne. Therefore, the pH of inflammatory acne lesions was determined prior to and after lesional acidification employing Herpifix© (Courage + Khazaka, Cologne, Germany), a microphoretic system. The pH was correlated with the number of acne lesions. A total of 30 volunteers with acne vulgaris participated in this crossover study applying either Herpifix or a dummy to inflammatory lesions. Prior to treatment, the pH of acne lesions was 5.7 ± 0.2 (mean ± SD) and 22 lesions (mean ± 10) were counted in an 8 × 8 cm^2 facial surface area. Fifteen volunteers (group A) used Herpifix first for 3 weeks and then the dummy, while the other group of 15 volunteers (group B) used the dummy first and then Herpifix. In group A, the lesional surface pH and number of lesions decreased ($p < 0.01$) initially. When the dummy was used over a second 3-week treatment period, the skin surface pH and number of acne lesions increased. Findings for group B were vice versa. When both groups were compared at the end of the study, a significant difference in pH values ($p < 0.001$) and the number of acne lesions ($p < 0.05$) was obtained. Herpifix may be considered as a new therapeutic option for inflammatory acne.

Key words: *Acne treatment, acne vulgaris, lesional acidification, skin surface pH*

Introduction

According to Braun-Falco and Korting (1), normal skin surface is known to have an acid pH (2). The relationship between this acid mantel and the resident flora has been studied intensively (3).

Furthermore, some of the biological activities of the stratum corneum are influenced by pH variations (4–6). A functional stratum corneum requires the combined action of many enzymes. All of these derive from the stratum granulosum and most of them are located in the intercorneal space (7,8). Two main groups of enzymes are differentiated: lipid modifiers and proteases. Both types of enzymes are important for barrier homeostasis and corneocyte desquamation. Stratum corneum chymotryptic enzyme, phospholipase A2, and steroid sulfatase are neutral enzymes and are activated at a pH of 7, whereas acidic enzymes (β-glucocerebrosidase, sphingomyelinase, acylcoenzyme A transferase) are activated at a pH of 5 (9,10). The existence of a pH gradient within the epidermis, with a neutral pH in the basal layer and an acid pH in the stratum corneum, is crucial in terms of the activation and inhibition of these mentioned enzymes (11).

Increased sebaceous gland activity, excessive growth of residential micro-organisms, as well as hyperkeratosis of the infundibulum are major pathophysiological components of acne vulgaris. Downing and co-workers hypothesized an essential fatty acid deficiency within the follicular epithelium, which may reason the follicular hyperkeratosis (12). At the time of their hypothesis, the importance of an acid pH for the activation of epidermal lipid synthesizing enzymes was not known. Barrier disturbances, inflammation and altered desquamation are influenced by pH variations (4–6). A lesional increase of skin surface pH may not

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only influence the growth of infundibular microorganisms, but also the fine-tuning of local, lesional stratum corneum enzymatic activities (3,13). Therefore, lesional pH may contribute to the pathogenesis of acne.

It is well known that superficial chemical peels (pH of 2–3), accompanied by the use of skin care products with a pH of 4, clear papulopustular acne without much irritation. Focus has been given so far to the keratolytic effect of either salicylic acid or alpha hydroxyacids, but not so much to their pka (acid dissociation constant) (14–16).

In the following study, papular or pustular acne lesions were subjected to acidification employing Herpifix®; the pH of the lesions was taken and acne lesions were counted prior to and after a 3-week treatment course. A total of 30 volunteers, aged between 20 and 26 years, with acne vulgaris participated in this crossover study employing Herpifix or a dummy thereof.

Materials and methods

The study was carried out at the University of Osnabrück, Germany, between October 2005 and March 2006. A total of 30 healthy volunteers (15 females and 15 males), mean age 25 years (± 3.9), enrolled with randomized assignment after informed consent.

A flat glass electrode (Mettler-Toledo, Giessen, Germany) attached to a precision pH meter (PH 900; Courage & Khazaka, Cologne, Germany) was used to measure skin lesional pH. The readings were taken in an air-conditioned room with the temperature set at 25°C. The lesional pH was measured by applying the flat glass electrode of the pH meter directly to the surface of the lesion and was allowed to equilibrate for 7 seconds (17). The skin pH was monitored between 11 am and 2 pm to avoid diurnal fluctuations (18).

Papules and pustules were counted on both cheeks in a fixed surface area employing an 8 × 8 cm template. Participants were white Caucasians (Fitzpatrick skin types I–II) to avoid racial differences in pH values (19). The female:male ratio was 1:1, with 15 males and 15 females participating in the study.

Herpifix is a battery-operated, micro-iontophoretic system with a central pin and a surrounding ring, using an electrical field with a very low current. The acidity of the treated area can be changed to below pH 2. Herpifix was originally designed to treat herpes labialis in its early development.

This blinded crossover design of the study included the home use of the Herpifix and a specially designed dummy thereof. After study inclusion, acne lesions on both cheeks were counted within a given 8 × 8 cm surface area, the pH values of acne lesions were taken and participants were instructed in the use and handling of Herpifix or the dummy thereof. Volunteers were told to use the Herpifix at least three times daily on given acne lesions. There was not much concern about participants' compliance as all of them were university students and were interested in the improvement of their skin disease. Volunteers were instructed not to use any other specific acne treatment during the course of the study. Initially, 15 participants were supplied with Herpifix (group A) and 15 participants with the dummy (group B). After the first 3-week treatment course, lesions were counted in the given 8 × 8 cm surface area, the pH was taken as described above and according to the crossover design of the study, group A was supplied with the dummy and group B was supplied with the Herpifix. At the end of the treatment course (i.e. after another 3-week period) the acne lesions were counted again and the pH of the lesions was taken.

Data were calculated with SPSS Base for Windows (version 16.0). The median and 25/75 percentiles were chosen as the standard for the descriptive statistics. Differences between groups were tested for their statistical significance employing the Mann–Whitney *U*-test for not normally distributed non-paired data. The Wilcoxon signed rank test was used to compare results in the course of each group. The chosen level of significance was $p \leq 0.05$.

Results

Prior to the Herpifix treatment, the pH of acne lesions ranged from 5.3 to 6.1. Group A ($n = 15$) revealed a mean lesional pH of 5.66 ± 0.24 (Figure 1) and a total of $n = 22.5$ (mean ± 10.1) papules and pustules in surface areas of 8 × 8 cm (right and left side of face) (Figure 2), while group B ($n = 15$) revealed a mean lesional pH of 5.72 ± 0.25 (Figure 1) and a total of $n = 21.6$ (mean ± 8.0) papules and pustules in both surface areas of 8 × 8 cm (Figure 2). There was no statistical difference in the number of lesions and the pH value between the two groups at the start of the study.

After the initial 3-week treatment course, the number of lesions had declined in group A to a mean value of 14.5 ± 5.7 ($p < 0.01$) while that of

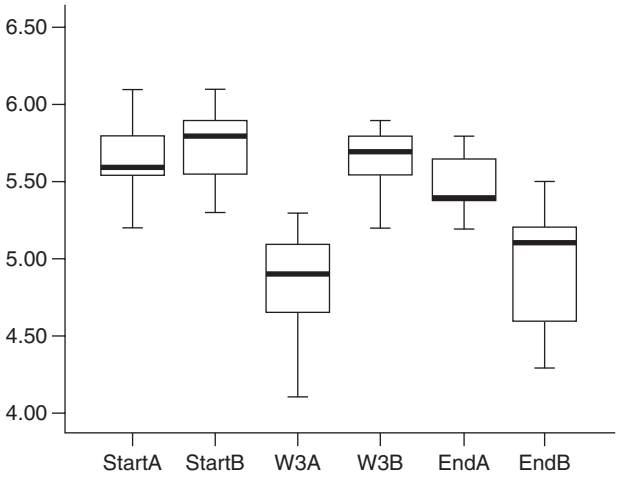

Figure 1. The pH values of group A: prior to a 3-week period use of Herpifix® (startA) and thereafter (W3A), and after crossover at 3 weeks followed by a 3-week period using a dummy (endA). The pH values of group B: prior to an initial 3-week period use of a dummy (startB) and thereafter (W3B), and after crossover at 3 weeks followed by a 3-week period using Herpifix (endB).

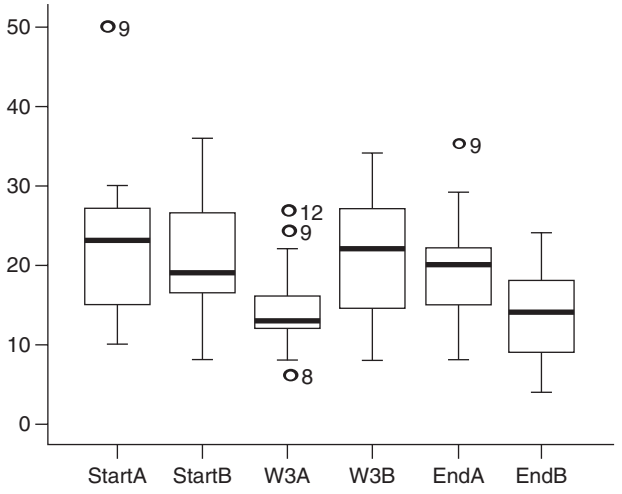

Figure 2. Total number of papules and pustules in a defined 8 × 8 cm facial area. Group A: prior to a 3-week period use of Herpifix® (startA) and thereafter (W3A), and after crossover at 3 weeks followed by a 3-week period using a dummy (endA). Group B: prior to an initial 3-week period use of a dummy (startB) and thereafter (W3B), and after crossover at 3 weeks followed by a 3-week period using Herpifix (endB).

group B remained unchanged (from $n = 21.6 \pm 8.0$ to 20.5 ± 8.0, NS) (Figure 2). The decrease in skin lesions in Group A was accompanied by a decrease in lesional surface pH (from 5.66 ± 0.24 to a mean pH of 4.84 ± 0.33, $p < 0.01$), while that of group B remained unchanged (from 5.72 ± 0.25 to 5.63 ± 0.19, NS) (Figure 1).

After the initial 3-week treatment course, the crossover point was reached: group A then received the dummy and group B received the Herpifix. Another 3-week treatment course followed before final measurements were taken.

After the total study duration of 6 weeks, final measurements revealed a mean lesional pH in group A of 5.48 ± 0.19 accompanied by a mean count of acne lesions of 19.9 ± 6.8.

After the total study duration of 6 weeks, a significant reduction in the number of lesions was noted in group B (from 20.5 ± 8.0 to 13.6 ± 6.0, $p < 0.01$) (Figure 2), accompanied by a decrease in mean lesional skin pH (from 5.63 ± 0.19 to 4.96 ± 0.39, $p < 0.001$) (Figure 1).

The Mann–Whitney *U*-test revealed a significant difference in pH values ($p < 0.001$) and number of acne lesions ($p < 0.05$) when both groups were compared at the end of the study.

Discussion

According to the results of this crossover study, Herpifix is another treatment modality of inflammatory acne lesions. The number of acne lesions decrease with the daily repeated use of Herpifix, accompanied by a decrease of lesional pH. The success of the treatment depends on its continuous usage (i.e. as soon as the treatment is stopped, inflammatory acne lesions revive). Hence, the treatment with Herpifix is accompanied by a slight sting, which the dummy does not have; most of the group A participants thought that the treatment pin they received at the time of the crossover was 'not functioning properly'. Because group B was used to the dummy at the start of the study, a comparison to the slightly stinging Herpifix could only be made by this group.

As only young adults of skin types I–II participated in the study, neither age nor sex will have influenced the data obtained. Endogenous and exogenous factors influence the pH of the skin surface (17,20,21). Further, skin pH is influenced on the anatomical site by numerous external factors; of which, the most important is skin cleansing. In order to avoid external factors which could affect the measured pH of skin lesions, participants were told not to use any topicals except for an acidic skin cleanser, which was to be used once daily, if desired. However, home treatments cannot be excluded completely.

The anatomical study site was the cheek, a body area rich in sebaceous glands. Sebum secretion may indeed affect the skin surface pH.

A significant increase in skin pH was shown in skin dryness (22). It has been postulated that skin dryness accompanied by an increased skin pH may influence the bacterial skin flora. While *Staphylococcus aureus* strains show an optimum growth at pH 7.5, *Propionibacterium acnes* reveals an optimal growth peak at pH 6.0–6.5. Prior to the start of the study, the pH of the acne lesions was 5.7 ± 0.2, which may have enhanced the growth of *P acnes*. Upon the Herpifix treatment, the lesional surface pH decreased to 4.84 ± 0.33, while 14.5 ± 5.7 lesions were counted. This positive correlation in *P. acnes* counts and skin pH may explain the clinical effect obtained with Herpifix on acne lesions. However, since an increase of skin surface pH disturbs the barrier and is accompanied by inflammatory reactions (3–6), lowering the pH in acne lesions may have more impact on the pathogenesis of acne than just on bacterial growth.

Management of acne vulgaris includes non-ablative chemical peels (23). The accumulative effects of more than two superficial peel treatments of facial acne do not affect the sebum secretion (24). However, superficial chemo exfoliation has not been linked sufficiently to the change of lesional pH, which is the subject of an ongoing study. Keeping the effect of an acid pH on bacterial growth as well as barrier homeostasis in mind, intermittent application of Herpifix in mild to moderate acne is reasonable.

The standard regimen for inflammatory acne lesions caused by *P. acnes* is topical erythromycin, which has an alkaline pH. Therefore, topical erythromycin preparations from a pharmacological point of view have a pH of above 7. Korting et al. (3) have influenced the use of topical erythromycin preparations for acne vulgaris on skin surface pH. Keeping in mind that the pH can only be measured in extractable water-soluble components, acne-related abnormalities in skin surface pH may be considered in future drug pharmacokinetics for topical acne treatment. The pH is defined as the negative logarithm (base 10) of the concentration of free hydrogen ions in aqueous solution. The neutral point equals 7, ranging from 0 (most acidic) to 14 (most alkaline).

Knowing the dramatic effect of age on the lipid solubility of many amphophilic drugs, the transcutaneous penetration of such compounds could be affected by the pH of the stratum corneum, the initial barrier. Charged substances will permeate intercellular lipids more than uncharged ones. Charged compounds may be more efficiently retained within the hydrophilic corneocyte.

If a neutral to alkaline preparation is applied, an increase of skin surface pH is accompanied by an increase of *P. acnes*, which may counteract the antibacterial effect of the ingredient. Furthermore, the prevalence and antibiotic susceptibility patterns of *P. acnes* strains were studied in acne patients. Patients treated with antibiotics (tetracycline, erythromycin, clindamycin, trimethoprim-sulfamethoxazole) revealed significantly more resistant *P. acnes* strains than the non-antibiotic control group. Therefore, according to these authors, long-term antibiotic therapy in acne patients should be avoided.

Further studies are required to link lesional bacterial growth and lesional pH to the extent of mild to moderate acne vulgaris.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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