Original Contribution

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Significant improvement in mild acne following a twice daily application for 6 weeks of an acidic cleansing product (pH 4)

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Summary

Background Cleansing products for acne should remove excessive sebum, reduce acne-related bacteria and improve inflammation.
Aims The aim of the study was to investigate a topical cleansing product containing glycolic acid with pH 4 in mild acne vulgaris.
Methods Sixty patients were recruited for this open uncontrolled clinical trial. The tested product was exclusively applied twice a day for 6 weeks. The efficacy was judged by a dermatologist according to the Leeds score after 3 and 6 weeks. In addition, efficacy and tolerability were judged subjectively by physician and patients.
Results Mild acne improved significantly after 6 weeks (baseline: 0.699 *vs.* day 42: 0.602; $P < 0.001$). Efficacy and tolerability were judged better by physician as compared with patients' assessment.
Conclusion In this clinical trial, a topical cleansing product containing glycolic acid with pH 4 improved mild acne significantly following twice-daily application for 6 weeks as monotherapy.

Keywords: acne vulgaris, AHA, antibacterial, clinical trial, glycolic acid, *P. acnes*

Introduction

The acidic skin surface pH of the stratum corneum is an essential component of the epidermal barrier protecting the skin against noxious stimuli from the environment.[1–5] Both the pH value on the skin's surface and the pH gradient in the stratum corneum are of great importance. This gradient controls the activity of pH-dependent enzymes, which regulate skin cornification, desquamation/cohesion, and homeostasis of the barrier function.[2,6] Free fatty acids derived from phospholipids as well as lactic acid, urocanic acid, and pyrrolidone carboxylic acid derived from proteins maintain the acidic pH.[2,4,7] The third and probably predominant mechanism to achieve an acidic pH is the NA+/H+ antiporter (NHE1) expression.[2,4] In addition, the pH also depends on exposure to environmental conditions as well as age, gender, anatomic site, or even the use of cosmetic products.[3,5] The effect of cosmetic products could be verified by comparing an acidic syndet and an alkaline soap in a cross-over study.[8] This is of importance as changes in the pH of the stratum corneum may either promote or alleviate skin diseases, for example, atopic dermatitis, acne vulgaris, or mycotic infections.[9–12] The pH has a great impact on the metabolism of microorganisms, especially *Propionibacterium acnes*. Studies have shown that the growth and activity of *P. acnes* can be reduced by lowering the pH value.[13–15] Therefore, to test the pH-decreasing capac-

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ity of glycolic acid in a cosmetic formulation, a clinical trial was performed, applying a glycolic acid containing oil-in-water emulsion (pH 4) to the volar forearm. It was shown that the pH of the treated skin surface decreased significantly from pH 5.2 ± 1.7 prior to application to 4.0 ± 0.3 just 10 min after application.[16] Furthermore, during the measurement period of 3 h, the pH remained significantly reduced. Moreover, the pH was lowered throughout the stratum corneum down to the layers of the vital epidermis.[16] Glycolic acid acts as a proton donor thus lowering the pH of the product containing glycolic acid as well as the pH at the site of application. Therefore, topical cleansing products containing glycolic acid and a subphysiological pH may be used to support acne treatment.[5,9,11,17]

The aim of this study was to investigate the safety and efficacy of a cleansing product containing glycolic acid with a pH of 4 as a medical device (class 2a) for treatment of mild acne vulgaris applied twice a day over a period of 42 days.

Materials and methods

The product under investigation was a certified medical device class 2a (CE-0499) containing H_2O, sodium C14-16 olefin sulfonate, sodium cocoamphoacetate, glycerin, sodium lauryl glucose carboxylate, lauryl glucoside, glycolic acid, parfum (fragrance), sodium chloride, PEG-120 methyl glucose trioleate, and propylene glycol. A mixture of mild, nonirritating and biodegradable surfactants was used. The pH value of 4 was adjusted by 1% glycolic acid. The study took place between April and June 2012. Sixty patients were recruited for this clinical trial by a dermatologist from the outpatient section of a dermatological clinic in Germany. Eligible patients were >16 years with mild facial acne corresponding to Leeds score 0.5, 0.75, or 1.00.[17,18] All participants provided written informed consent before participating in the study. Parents or legal guardians signed the consent for their children. The study was conducted in accordance with the guidelines for good clinical practice and the Declaration of Helsinki. Exclusion criteria were as follows:

- History of hypersensitivity to one of the ingredients of the study preparations.
- Refusal of cosmetic preparations other than hair shampoos to come in contact with facial skin.
- Topical treatment of the facial skin during or up to 1 month before the start of the study.
- Use of systemic pharmaceuticals during or up to 2 months before the start of the study.
- Alcohol and/or drug abuse.
- Incapacity of duly participating in the study procedures.
- Participation in another study within the past 4 weeks and/or simultaneously to this study.
- 4 applications missed from the total 42 ± 4 applications during 21 ± 2 days.
- Use of acne-influencing contraceptives.

The study was performed as a monocentric, open, uncontrolled, nonrandomized clinical trial. At the prestudy visit (visit 0), comorbidities and prior treatments of each participant were documented. Patients who had medical acne treatment directly prior to the study had to undergo a wash-out phase for 4 weeks after the prestudy visit. At day 0 ± 3, the initial skin inspection followed (visit 1) with documentation of the Leeds scores. After inspection, the cleansing product and a patient's diary were handed to the patients for the first period of the study of 21 days (day 21, visit 2). The diary was used by the participants to record how their skin felt as well as any adverse effects using the graduation "none", "mild", "moderate," and "severe" after each application. At the end of the study, the participants were asked to give an overall subjective assessment of the product's safety and efficacy using the scale of "very good", "good", "moderate," or "poor". Adverse effects which occurred during application of the medical device and which the investigating doctor related to the application had to be reported to project management within 24 h (at the latest on the next working day).

According to the investigation plan, 86.4 g (mean; range 23–184 g) of the medical device was used up to day 21 (visit 2) and 89.3 g (mean; range 36.5–165 g) up to day 42 (visit 3). After 21 ± 2 days, the first clinical inspection took place with documentation of the Leeds scores and possible adverse effects (visit 2). During this visit, the packaging of the medical device was taken back and weighed, and a second one was handed to the participants for the second part of the study. After 42 ± 2 days, the second inspection took place (visit 3), again with documentation of the Leeds scores and adverse effects. The packaging was taken back and weighed again. A subjective evaluation of clinical efficacy and safety was made by physicians as well.

Safety analysis

This analysis included all patients who applied preparations during the course of the study: $n = 60$ participants.

Intention-to-treat analysis

This analysis was conducted for all participants whose data with regard to the primary endpoint (Leeds score) were at least recorded at the beginning and end of the study. According to this, $n = 59$ were included in this analysis.

Per-protocol analysis

All participants with complete documentation of their data with regard to the primary endpoint (Leeds score) and with no violation of the investigation plan were included in this analysis. According to this, $n = 50$ were included.

Data collection and evaluation were carried out in accordance with GCP/ICH criteria. Evaluation of the data was performed by SAS version 9.2 for Windows. As this was an open, uncontrolled clinical trial, no statistical analysis plan was made. Therefore, all statistical tests performed are of descriptive and exploratory character. For the probability of the incidence of adverse events, two-sided 95% confidence intervals were estimated.

Results

The youngest patient was 16 years old and the oldest 56 years old (ITT, mean: 26 ± 8.4 years) and 47 years old (PP, mean: 25 ± 7 years), respectively. In total, there were 32 women (54.2%) and 27 men (45.8%) in the ITT group and 26 women (52%) and 24 men (48%) in the PP group. Twenty-four (41%) participants had facial acne corresponding to a Leeds score of 0.5, while 23 (39%) had a score of 0.75 and 12 (20%) a score of 1.0 (Fig. 1).

Efficacy

At day 21 (visit 2), there was no significant improvement in the Leeds score compared with the baseline (visit 1) neither in the ITT nor in the PP analysis. At day 42, there was a statistically significant improvement compared with visit 1 in the ITT as well as in the PP analysis. Following twice daily application for 42 days, the Leeds score significantly improved statistically (ITT, $P = 0.0008$). Twenty-three (40%) of the 59 ITT patients showed an improvement in 1 scale point. Six of 12 patients with an initial score of 1 improved to 0.75; 13 of 23 patients who had a starting score of 0.75 showed a decrease down to 0.5, and 4 patients of 24 with an initial score of 0.5 had an improvement to 0.25 (Fig. 1). The average Leeds score of the ITT group improved from 0.699 to 0.602 (Fig. 2). Improvement was also statistically significant in the PP analysis ($P = 0.0062$). Eighteen (31) of the 50 patients had an improvement in one point on the Leeds score scale. Five of 11 patients with a starting Leeds score of 1 showed an improvement to 0.75, nine patients of 19 with an initial value of 0.75 improved to 0.5, and four patients of 20 who had a Leeds score of 0.5 at visit 0 showed an improvement of up to 0.25 at visit 3. The average Leeds score decreased after 42 days of therapy from 0.705 to 0.615.

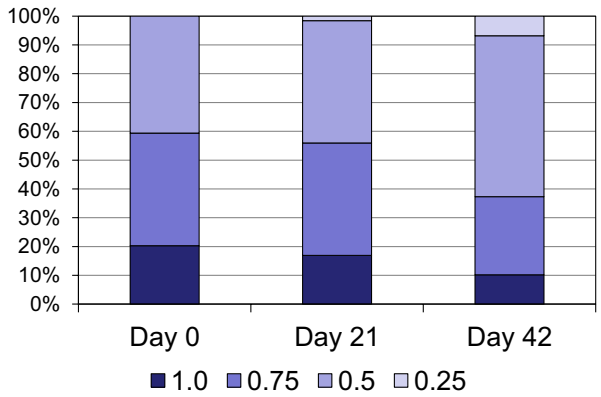

Figure 1 The individual Leeds score of the ITT population is shown over application time. There is a continuous decrease in the individual Leeds score from day 1 to day 21 and to day 42. At day 42, only 10.2% of the patients exhibit a Leeds score of 1.0 and 27.1% of 0.75, respectively, as compared to day 1 (20.3% and 39%, respectively). The improvement from day 1 to day 21 as well as from day 1 to day 42 is statistically significant ($P < 0.001$; Fisher's Exact Test).

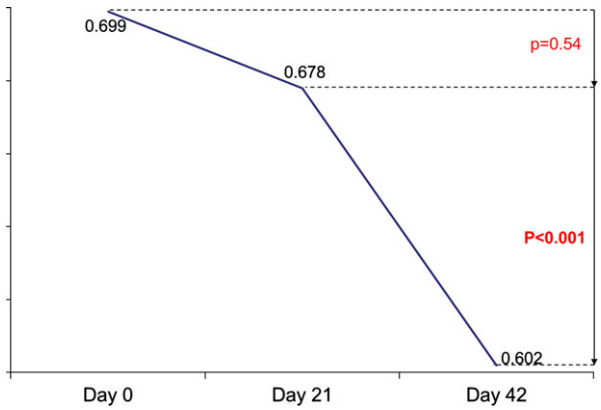

Figure 2 There is a significant improvement in the overall Leeds score after 42 days following a twice daily application of the. Even 23 of 59 patients improved by 1.0 of the Leeds score ($P < 0.001$; ITT population).

Table 1 Subjective evaluation (%) of physician and patient regarding efficacy and tolerability at the end of the study

	Efficacy				Tolerability			
(%)	Very good	Good	Moderate	Poor	Very good	Good	Moderate	Poor
Physician	10.2	61.0	27.1	1.7	23.7	54.2	22.1	0
Patient	13.6	47.5	23.7	15.2	23.7	42.4	27.1	6.8

Moreover, the patients and physicians documented a significant efficacy of the cleansing product in the subjective assessment (Table 1). Sixty-one percentage of the patients in the ITT group and 71% of the physicians judged the overall efficacy of the acidic syndet as "good" or "very good".

Safety and tolerability

All 60 patients were included in the safety analysis. Adverse effects following application of the cleansing product (pH 4) for 42 days were expected and comprised a feeling of skin tightness (57%), scaling (26%), redness (22%), burning (17%), and itching (11%). Eighty-six percentage of all patients reported adverse effects as being mild, whereas 12% considered them as moderate and even 2% as severe. The intensity of the reported adverse effects decreased or disappeared over the course of application.

The majority of both the patients (66%) and the physicians (78%) assessed the safety of the cleansing product as "very good" or "good". The physicians generally assessed the performance of the medical device more favorably than the patients. However, only 6.7% of the study participants considered the tolerability and safety as poor.

Discussion

The present clinical trial proved the clinical efficacy of the investigated medical device of a skin cleanser with a pH of 4 in mild facial acne. Not surprisingly, the efficacy was judged by the majority of patients as "very good" or "good".

Cleansing products consisting of alkyl polyglycosides or other mild surfactants are well known for cleansing in dermatology because they are less irritating than soaps and have a mild lipid balancing capacity.[5,8,19]

The acidic syndet gel of the present study with a pH value of 4 is composed of a mixture of mild surfactants that emulsify comedogenic and inflammatory decomposition products and remove them from the skin surface without irritation. Due to the pre-adjusted pH value of 4 by the α-hydroxy acid (glycolic acid), the acidic syndet may lower the pH value of the skin surface and may thus impair growth conditions for bacteria like *P. acnes*. Due to the low content of about 12% active matter and the combination of mild surfactants, the gel is well suited to gently cleanse the face. Foaming is only moderate, and this is desirable for this kind of product. The combination of sodium C14-16 olefin sulfonate, sodium cocoamphoacetate, lauryl glucose carboxylate, and lauryl glycoside was not only chosen because of its good tolerability but also from a technical point of view. These surfactants are stable against hydrolysis at pH 4, which is very important for attaining an acceptable shelf-life period of the product.

The mechanism of action of this medical device is due to the use of surfactants and, very likely, an acidic pH. Just recently, we showed the efficacy of a 10% glycolic acid containing oil-in-water emulsion in a double-blind, randomized trial in mild acne.[17] The antibacterial effects of an acidic pH are well described in the literature and confirmed by other investigations.[5,11,13–15] In addition, an acidic pH is responsible for the exfoliating effect of AHAs as it reduces the coherence of superficial and also follicular corneocytes.[20,21] Therefore, a benefit to whatever extent of the use of a cleansing product with pH 4 could be expected. However, application of this cleansing product twice a day over a period of 6 weeks even leads to a visible improvement with a statistically significant change of the mean Leeds score from 0.699 down to 0.602 (ITT analysis, $P < 0.001$). Altogether, 23 patients achieved a decrease in the Leeds score by one grade, which is quite remarkable. This positive result after only 6 weeks of application is supported by the subjective evaluation of the physicians and patients. 10.2% of the physicians assessed it as "very good" and 61.0% of them assessed it as "good". Interestingly, there is a small difference between patient and physician regarding efficacy with respect to categories "good" and "poor". Unfortunately, the patients considering the efficacy poor did not explain their assess-

ment. As the percentage of patients considering the tolerability as "poor" is smaller, most likely expectations with respect to efficacy of the product were not met. In particular, in the group with an initial Leeds score of 0.5, only 4 were responders, whereas 20 were nonresponders. Probably, a further improvement is difficult to be recognized for a nontrained individual (patient). It would be interesting to see the results after even longer application times, for example after 3 months, particularly because it is known that cosmetic rinse-off and additional leave-on products improve mild acne and even increase the quality of life in acne patients.[22–25]

The tested cleansing product induced adverse effects like burning, itching, tightness, redness or scaling. These were expected as they are part of the effect and were reported to be generally mild in nature. As the ingredients are well known and have been thoroughly tested either as a substance on its own or in cosmetic formulations, no unexpected adverse effects occurred. The concentration of glycolic acid used in this product is only 1.4%. Thus, eyes and nostrils should be spared.

In this clinical trial, an acidic cleansing product with pH 4 significantly improved mild acne following application twice a day for 6 weeks as monotherapy. As the skin surface's pH in acne patients is increased, lowering this is likely to improve acne by reducing corneocyte cohesion and inhibiting growth of acne-related bacteria. As cleansers are already recommended as therapeutic concomitants in various dermatological disorders,[26] we recommend using acidifying rinse-off and leave-on products alone or in conjunction with standard acne medication depending on acne severity.

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