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A rapid method to clinically assess the effect of an anti-acne formulation

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Synopsis

Historically, clinical evaluation of acne treatment has been based on direct visual assessment and the counting of lesions over a period of several weeks of treatment. However, with advancing technology there has been ever-increasing speed in the effectiveness of these treatments. To successfully assess these faster treatments, acne pathology needs to be evaluated in a shorter time frame. The object of these studies was to develop techniques to evaluate individual acne lesions in a shorter time frame and to assess speedier treatment technologies.

Ten healthy volunteers with acne lesions on their upper backs were recruited for the study. Two inflamed acne lesions were selected for each treatment, along with lesions to be left untreated, on each volunteer. Each lesion was marked, photographed, and visually graded. A skin surface microscope (Scopeman) was used to visualize size and to grade the lesions by two experts every day for five days. The sites were treated once a day for the course of the study.

There was a remarkable reduction in the size and erythema of acne lesions after treatment with the acne formulation as compared to the untreated and vehicle-treated lesions. Individual lesions, both treated and untreated, appeared resolved in 14 days. This resolution can be noticeably accelerated by topical treatments. We have developed a simple and faster clinical method to evaluate the effects of topical anti-acne technology.

INTRODUCTION

Acne vulgaris is one of the most common skin diseases in human beings and affects up to 90% of adolescents and young adults at some point in life. One third of these individuals may require medical treatment due to the severity of the condition. A small percentage of these patients will be left with lifelong post-acne scars. These factors contribute to acne having a major impact on the quality of life and being a major socioeconomic problem.

Acne vulgaris is a multifactorial disease that has at least four distinct pathological factors. These four factors are excessive sebum production, hyperproliferation of the follicular epithelium, bacterial infection, and localized inflammation. Each of these components of the etiology of acne is not mutually exclusive of the others. One theory of acne suggests that these components are in fact sequentially dependent.

The pathological process starts with the production of excessive sebum. Sebum lipids are a complex mixture of squalene, wax esters, and triglycerides. The triglycerides can be

metabolized by bacterial enzymes to glycerol and free fatty acids. Excessive sebum secretion and loosely bound corneocytes clog pores and create an anaerobic environment where anaerobic microorganisms multiply and eventually provoke inflammatory reactions. Excessive sebum production has been attributed to androgen levels. Several clinical observations clearly indicate a causal role for androgens in acne. Androgens have been shown to increase the size and output of sebum of the sebaceous glands (1). Acne begins to develop with the increase in androgens during the prepubertal period. Conversely, antiandrogens have been shown to reduce sebum lipids and to alleviate acne.

Acne is also characterized by improper epidermal differentiation of the lower portion of the infundibulum of the sebaceous follicle. The keratinocytes lining the infundibulum are hyperproliferative compared with normal skin. This improper epidermal differentiation leads to a clogged pore. This clogging of the pore creates a micro-environment favorable for the growth of acne.

The excessive lipids and improper differentiation of the keratinocytes in the follicle encourage bacteria growth and cause a weakening of the skin barrier in this follicle. This allows the excessive bacteria to migrate into the skin and contribute to the inflammation observed in the final stages of the acne process (1,2). The primary pathogenic agent implicated in the development of inflammatory as well as non-inflammatory acne is *Propionibacterium acnes* (3). *P. acnes* is included in a family of anaerobic, non-spore-forming gram-positive rods. The 1960s saw the use of antibiotics to treat acne by reducing *P. acnes;* however, in the last two decades several antibiotic-resistant strains have emerged (4,5). In addition to antibiotics, topical benzoyl peroxide and salicylic acid have consistently been found to be effective in reducing acne lesions (5,6).

The final phase of comedone formation is the inflamed lesion. The bacterial infiltrate into the skin triggers inflammatory mediator production and cellular infiltrate. A variety of inflammatory mediators have been described in the acne lesion. These include IL-1 alpha, IL-1 beta, and substance P (7). In addition, there is a reported increase in lymphocytic infiltrate and neutrophil infiltrate into the follicular region (8). This also contributes to the inflammation associated with the acne lesion.

Clinical assessment of the efficacy of acne treatment has been largely based on global expert assessment, lesion counts or patient assessment (7–9). These techniques have been enhanced with the use of modern photographic techniques. However, these clinical assessments still require the counting of lesions and the documentation of shifts in the total number of lesions to determine the efficacy of a topical treatment. This requires many weeks of the continued use of a treatment modality to observed shifts in the total number of lesions. In order to speed the evaluation process we have developed a technique to evaluate individual lesions.

MATERIALS AND METHODS

The treatment regimen consisted of the following materials: a simple foam cleanser, a toner (2% salicylic acid), and an oil-in-water lotion containing benzoyl peroxide. All three products were designed to address the four components of acne: keratinization, bacteria, sebum control, and inflammation. To address each of these issues we added the following ingredients: (a) n-acetyl glucosamine, used to accelerate desquamation; (b) decanoic acid, used for its antimicrobial properties; (c) saw palmetto extract, used to

suppress 5 alpha reductase and therefore sebum production (10); (d) hoelen extract, used to inhibit phospholipase A2 to suppress inflammation (11); and (e) resveratrol, a cyclooxygenase inhibitor, used to suppress inflammation (12). This product also contained 2.5% benzoyl peroxide (13).

CLINICAL

Ten female volunteers, between the ages of 18 and 50, were recruited from the local population. All subjects were of normal health with no evidence of acute or chronic disease other than acne. Written informed consent was obtained from each volunteer before entrance into the study. The panelists were not on any antibiotic, antihistamines, retinoids, anti-inflammatories, steroid therapy, or benzoyl peroxide and/or salicylic acid treatment for at least two weeks prior to commencement of this study. The subjects were not under the care of a dermatologist and were not on any acne treatment for at least one month before the study started. Pregnant or lactating females were excluded.

The panelists exhibited acne with at least four acne lesions on the upper back, where the minimum distances between lesions was approximately 4–6 cm. Two inflamed acne lesions were selected for each treatment and one to be left untreated. Each lesion was marked, photographed (14), and graded (15,16). A skin surface microscope (Scopeman) was used to visualize, size, and grade the lesions by two MDs at the testing lab. The lesions were treated and photographed every day for seven days (excluding Saturday and Sunday).

RESULTS

The lesions were chosen for maximum erythema and size. Each of these immediately appeared to resolve and lessen with each 24 hours of observation. Within seven days the size and inflammation was back to normal in the untreated lesions.

The regimen containing multi-prong technologies caused a significant immediate reduction in the size of the individual lesions. As observed in Figure 1, there was a distinct reduction in acne lesion size in the individual lesions treated with the regimen. This reduction in size occurred within two to three days.

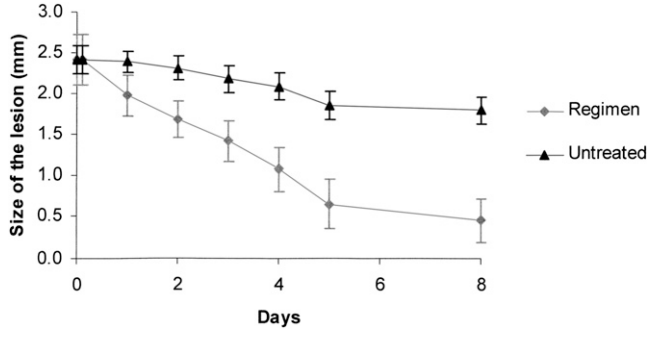

Figure 1. Average size of individual acne lesions in millimeters. Measurements were taken daily for eight days (excluding Sunday) for a control untreated lesion (black bars) and a treated lesion (grey bars). The area under the curve was 10.68 cm for the treated lesion and 15.37 cm for the untreated lesion (p = 0.0076).

The individual lesion's erythema and inflammation was also reduced by the multi-prong treatment. The degree of inflammation on the acne sites is reported in Figure 2. As observed in Figure 2 there was a marked reduction in acne lesion inflammation after two and three days for lesions treated with the regimen. The regimen appeared to be more effective in reducing acne-induced erythema having an area under the curve of 14.37, which is 11% less than the untreated control after 24 hours. This increased efficacy is clearly shown by the distinct reduction in acne lesion size and erythema on the site treated with the four-prong approach over time. The regimen reduced lesion size by 70% and erythema by 65% within six days of treatment.

DISCUSSION

The clinical assessment of acne treatments has historically been based on global evaluation of the patient or the lesion counts. These methods require long-term treatment and multiple time points to evaluate the treatment's effectiveness. However, recently developed treatment modalities, e.g., lasers, work in a shorter time frame, and these methods therefore require evaluation methods that are accurate on a shorter time scale. There is also a growing consumer interest in products that work in hours or days as opposed to weeks. This requires an understanding of the life cycle of individual comedones.

Previously it has been reported that a comedone cycle has a lifespan of 12–14 days (17). We also observed that individual comedones appear to have a lifespan of about 12–14 days on average. The acne lesion will naturally resolve over this time and can be noticeably improved in days. The lesions appear to be largest and most inflamed at day 7 or at the midpoint of the cycle. This resolution can be improved or accelerated by conventional treatments. Improvement can therefore be measured by the speed of resolution of the individual lesions and not only by a global score or total lesion count.

Based on the confines and conditions of this study, there was a distinct reduction in acne lesion size and erythema on the site treated with the new regimen within days of treatment. This regimen appeared to be the most effective in reducing acne lesion size, with over 80% of the lesion size and erythema alleviated within six days of treatment.

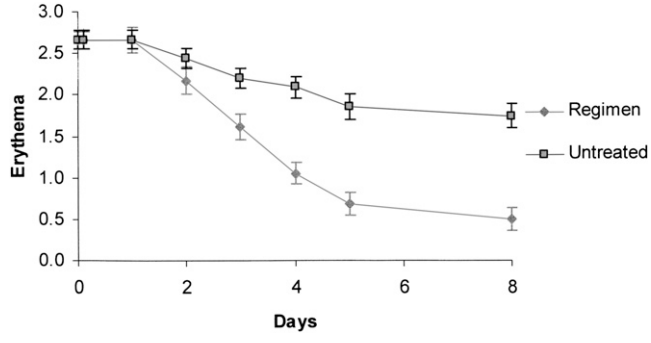

Figure 2. Average erythema of individual acne lesions measured daily for eight days (excluding Sunday). Erythema was assessed as described in Methods on a scale of 1–3 by an expert for a control lesion (black bars) and a treated lesion (grey bars). The area under the curve was 12.41 cm for the treated lesion and 16.09 cm for the untreated lesion (p = 0.0271).

CONCLUSION

We have developed a method to evaluate acne treatments that can reduce individual lesions in days as opposed to weeks. This method will help to assess new treatments and thereby improve the treatment design.

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