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Original Article

A three-stage strategy in treating acne vulgaris in patients with atopic dermatitis- a pilot study

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Abstract

Background Heightened susceptibility to skin infection occurs in patients with atopic dermatitis because their skin has a poor barrier against microorganisms. Acne is the most common skin condition worldwide. However, the lack of full understanding of its pathogenesis, and the high risk of scarring as a sequel, necessitates continuous trials to reach effective and rapid control. Thus the aim of this study was assessing the effectiveness of a newer treatment strategy in treating acne in patients with atopic dermatitis.

Patients and methods Ten female patients with atopic dermatitis suffering acne of moderate to severe grades, followed a three-stages treatment strategy. Stage I aimed at effective control of the inflamed acne lesions, stage II at minimisation of scarring and postinflammatory hyperpigmentation, while stage III aimed at naturally nourishing facial skin for cosmetic purpose.

Results Stage I regimen induced marked and rapid disappearance of acne lesions. Moreover, the stage II regimen caused marked diminution of scar lesions and hyperpigmentation. During stage III, facial skin showed a silky touch with brighter appearance**.**

Conclusion The three-stage strategy is a successful and safe method in effectively treating acne in patients with atopic dermatitis and in improving the facial skin status**.**

Keywords
Acne vulgaris, atopic dermatitis, treatment strategy.

Introduction

Acne is a typical condition of adolescence and is caused by multifactorial events. Although there has been much debate about the direct involvement of bacteria, *Propionibacterium acnes* is now believed to contribute to the inflammatory stages of the condition, and thus initiate the inflamed lesion.[1]

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Drug regimens that affect these etiologic factors have been shown to improve acne. In particular, antibiotic based treatment regimens are considered by many as the first-line treatment in topical and systemic therapies for acne.[2] Benzoyl peroxide is a bactericidal agent that has proven to be effective in the treatment of acne. In acne, employing multiple topical agents that affect different aspects of acne pathogenesis can be useful.[3]

Scarring is the most unfortunate and undesirable sequel of acne, because once formed, it is not amenable to pharmacological treatments and requires invasive procedures.[4,5] The salicylic

acid peel had sustained effectiveness and fewer side effects.[6] Moreover, they proved to be beneficial in whitening the face of Asian patients with acne and postinflammatory hyperpigmentation.[7]

The role of nutrition in acne still remains controversial.[8] Dietary interventions using low-glycemic load carbohydrates may have therapeutic potential in the treatment of acne because of the beneficial endocrine effects of these diets.[9]

The primary goal of this study was to evaluate the response of patients with atopic dermatitis suffering from moderate to severe acne vulgaris not responding to other conventional treatment, to a new three-stage treatment strategy with diet control together acting on the three factors often incriminated in acne pathogenesis i.e. excessive sebum production, sebaceous duct obstruction and infection. In addition, we tried to recommend a possible solution to the problem of acne scarring and postinflammatory hyperpigmentation.

Patients and methods

A total of 10 female patients aged 18 to 25 years were enrolled in this pilot study. The study was performed in accordance with the Declaration of Helsinki (South Africa, 1996 amendment) and good clinical practice guidelines. Inclusion criteria required patients with atopic dermatitis suffering from moderate to severe acne graded according to the "Comprehensive Acne Severity Scale" (CASS) by Tan *et al*. 2007.[10] No history of topical corticosteroids use on affected regions with acne and no previous systemic steroids intake were assured during history taking. Affected lesions with acne showed no clinically evident atopic dermatitis. Moreover, no previous treatment with any of the formula used in this study was assured. No history of allergy to any of the ingredients of the medications, scrub or natural products used was emphasized. None of the patients was receiving oral contraceptives, and they were neither pregnant nor lactating. Facial make-up was halted all through treatment duration. All cases not fulfilling these criteria were excluded from this study.

Study protocol

This open-label unblinded study consisted of three stages:

Stage I (from 3-5 weeks duration)

1. The face was washed with a specific soap for acne and the other affected sites were gently cleaned with a wet towel. Vigorous rubbing was forbidden.
2. A mixture was applied on acne lesions only, formed of benzoyl peroxide 10% gel + hydrocortisone cream in case of facial acne OR mometasone furoate 0.1% cream for acne on other affected sites + fusidic acid 2% with betamethasone valerate 0.1% cream + petroleum jelly (50g) for 90 minutes during weekdays (to be extended to 4 hours during the weekend and vacations provided in both cases, that patient was not exposed to sunlight to guard against photocutaneous reaction).
3. The face was washed with a specific soap for acne and the other affected sites were gently cleaned with a wet towel. Vigorous rubbing was forbidden.
4. Topical erythromycin solution 2% was applied on the acne lesions by the aid of

a cotton piece and left for 60 minutes during weekdays (to be extended to 4 hours during the weekend and vacations provided in both cases, that patient was not exposed to sunlight to guard against photo- cutaneous reaction).

5. The face was washed with a specific soap for acne and the other affected sites were gently cleaned with a wet towel. Vigorous rubbing was forbidden.
6. A mixture was applied on acne lesions only, formed of benzoyl peroxide 10% gel + hydrocortisone cream in case of facial acne OR mometasone furoate 0.1% cream for acne on other affected sites + fusidic acid 2% with betamethasone valerate 0.1% cream + petroleum jelly (50g) for 90 minutes during weekdays (to be extended to 4 hours during the weekend and vacations provided in both cases, that patient was not exposed to sunlight to guard against photo- cutaneous reaction).
7. The face was washed with a specific soap for acne and the other affected sites were gently cleaned with a wet towel. Vigorous rubbing was forbidden.
8. Topical erythromycin solution 2% was applied on the acne lesions by the aid of a cotton piece and left till the next morning.

Stage II (from 3-5 weeks duration)

1. The face was washed with the specific soap.
2. Daily facial use of apricot scrub which was left for 2 hours and then the face was washed thoroughly with warm water. No evidence of allergy or cross reactivity to any of the ingredients was assured in each patient before the use of this scrub.
3. The other affected sites of the body were cleaned with wet towel.
4. Another mixture was applied on the whole lesion site twice daily for at least 2 hours (facial and non-facial), it was formed of salicylic acid combined with betamethasone dipropionate and silver sulphadiazine 1% (patient was not exposed to sunlight to guard against photo-cutaneous reaction). (None of those patients was allergic to aspirin, nor were they pregnant or lactating)

Stage III

1. The face was washed with the specific soap.
2. The daily facial use of apricot scrub which was left for 2 hours and then the face was washed thoroughly with warm water.
3. A mask made of one soup spoonful of full cream yogurt + one teaspoonful of honey + one teaspoonful of almond oil was mixed together, put in the refrigerator for an hour, applied to the face daily (except the peri-orbital regions) and was left for 2 hours. No evidence of allergy to any of these elements was assured in each patient before the use of this mask.
4. The face was then washed with warm water only.
5. Warm almond oil was applied by a cotton piece on the face 30 minutes before night sleep which was rubbed gently and cautiously and left till the next morning. These steps of stage III were done daily for a month, every other

day for another month, three times a week for a third month and then once weekly thereafter.

One tablet of erythromycin 250 mg was prescribed daily after each meal for 3 months.

One tablet of levocetrizine dihydrochloride 5 mg was prescribed daily before sleeping by night for 3 months.

Chocolates, sweets, pickles, pepper, paprika and curry were totally forbidden throughout the study.

Clinical assessments

Patients were seen at baseline, to assess acne site(s), grading, previous therapy and allergic status. The follow up visits included clinical evaluation of acne status and assurance of lack of any complications from therapy.

Results

Patient characteristics

Ten females with median age 20.6 years (range, 18-25 years) with moderate to severe atopic dermatitis according to SCORAD index associated with other allergic diseases suffering from moderate (6 cases) to severe (4 cases) acne vulgaris were enrolled in this study (**Table 1**), and followed a new three-stage treatment strategy with diet control.

Most of those patients showed recurrence of inflammatory acne lesions after stoppage of other conventional acne treatment formulae. However, neither of formulae used in this strategy was ever used before by any of those patients. Moreover, to assure efficiency of this strategy, all treated patients used the same trademark of medication, despite lack of financial benefit or sponsorship from any pharmaceutical company.

Treatment efficacy evaluation

Patients in stage I were followed up after 3 weeks, and in case of total disappearance of inflammatory acne lesions, patient was then shifted to stage II, if not (only in the 4 cases with severe acne) treatment of stage I was continued for another 2 weeks and patient condition was then re-evaluated, and by disappearance of acne lesions in those 4 cases, stage II regimen was started. One of those 4 cases had not followed the diet control policy; she reported flaring up of facial inflamed acne lesions 2 weeks after start of therapy following 2 days of chocolate and pickles intake. Patient stoppage of this food stuff was followed by improvement, but on her 3 weeks follow up visit, there were still acne lesions and thus additional 2 weeks therapy was recommended with reassurance of complete diet restriction. Two weeks later, complete resolution was noted and patient started stage II regimen (case number 3).

Patients in stage II were followed up after another 3 weeks. In case of improvement of the scars and postinflammatory hyperpigmentation, patients were then shifted to stage III, and if not; treatment of stage II was continued for another 2 weeks (only in those 4 cases with previous severe acne and who required prolongation of stage I) and patient condition was then re-evaluated and they started stage III regimen.

Table 1 Demographic and clinical data of treated cases.

Case number	*Age (yrs)*	*Duration of acne (years)*	*Site*	*Grading*	*Stage I Duration (weeks)*	*Stage II Duration (weeks)*	*Complication*	*Allergic Disease(s)*
1	20	6	F	Moderate	3(+3 days treatment of facial complication)	3	Facial erythema, mild edema, burning sensation and fine desquamation	AD,AR,AC
2	18	6	F,B,C	Moderate	3	3	None	AD, BA,AR
3	19	2	F	Severe	5	3	None	AD, AC
4	23	5	F	Severe	5	3	None	AD,AR
5	21	6	F,B	Severe	5(+5 days treatment of facial complication)	5	Facial erythema, mild oedema, burning sensation and fine desquamation	AD
6	20	8	F,B	Severe	5(+5 days treatment of facial complication)	5	Facial erythema, mild oedema, burning sensation and fine desquamation	AD
7	25	3	F,B	Moderate	3	5	None	AD
8	20	3	F	Moderate	3	5	None	AD
9	21	5	F,B,C	Moderate	3	3	None	AD
10	19	5	F,B,C	Moderate	3	3	None	AD,AR

F=face, B=back, C=upper chest
AD=atopic dermatitis, AR=allergic rhinitis, AC=allergic conjunctivitis, BA=bronchial asthma

Tolerance and safety evaluation

In general, treatment regimen was well-tolerated with only the occurrence of facial erythema, minimal edema, burning sensation accompanied by fine desquamation of the cheeks in 3 cases (one with moderate acne and two with severe acne) immediately after the start of stage I therapy. Those 3 patients unfortunately applied the mixture on the whole face and not just on the acne lesions. To those patients, the already prepared mixture was stopped and replaced by another mixture with the same constituents as the first but devoid of the benzoyl peroxide. Also topical erythromycin lotion was temporarily stopped. This step aimed at controlling the side effect by the steroid creams in the mixture and oral already prescribed antihistaminic, meanwhile avoiding sudden discontinuation of acne therapy to guard against recurrence. Those 3 patients were asked to visit the Unit daily for follow up. Complete resolution of this side effect occurred within 3-5 days, thereafter; the first prescribed mixture was restarted and used only on the acne lesions with no change in the strength of the used benzoyl peroxide. This policy caused rapid and successful resolution of the side effect. Those

patients were strictly supervised and they reported no other complication.

Neither correlation of severity of allergic status and acne severity nor the latter response to therapy was done because of the limited number of studied cases.

Discussion

Many important documented facts guided the choice of therapy used in stage I: firstly, the massive colonization of skin of atopic dermatitis patients with *Staphylococcus aureus* in comparison with healthy controls[11-13] proved to respond well to topical fusidic acid that reduces the density of *S. aureus* without increasing fusidic acid-resistant *S. aureus*.**[14]** Moreover, the new combined fusidic acid-betamethasone formulation eliminates bacteria originally present in these skin lesions,[15] and relieve the dryness of atopic dermatitis skin. [16] As the role of fusidic acid in acne is undeniable,[17] thus the addition of this formula seemed necessary.

Secondly, topical antibacterial agents are an essential part of the armamentarium for treating acne vulgaris.[18] Topical erythromycin is one of the most commonly used agents in acne patients.[17,19-26] It reduces the capacity of *P. acnes* to produce neutrophil chemotactic factors, thus it has an additional anti-inflammatory action.[27]

Thirdly, guided by the recent consensus recommending that topical antibiotics should not be used alone due to the potential for bacterial resistance and relatively slow onset of action,[28] 10% benzoyl peroxide gel was added, aiming at benefiting from its mild comedolytic and keratolytic actions, effectiveness against antibiotic-resistant and antibiotic-sensitive bacteria. The absence of recurrence of acne lesions from any of our patients matches with results from similar studies, and emphasizes the mainstay role of this drug in acne treatment and the importance of combined therapy.[29-35]

Skin irritation is the most common side effect of benzoyl peroxide that often occurs at higher concentrations and tends to decrease with continued use.[36] Topical antibiotics can cause local irritation to some extent[37] in addition, to the special skin situation of the treated cases (xerosis), that is known to be easily irritated, even by pharmacy cosmetic products considered to be innocuous or even beneficial.[38] Those cases who applied the mixture on the whole face experienced irritant dermatitis. Thus this disagrees with recommendation by Thiboutot in 2000,[39] advising that all topicals should be applied to the entire face rather than to individual lesions.

Fourthly, the anti-inflammatory effect of steroids was evaluated on patients with acne. Although some reports[40] showed no significant change in lesion counts, however, other studies[41,42] showed that steroids can be effective in all grades of acne. The result at this stage level agrees with other reports that emphasize the usefulness of employing multiple topical agents that affect different aspects of acne pathogenesis.[3,43]

Fifthly, patients were suffering from xerosis, and as topical medication penetrates a moist stratum corneum from 10 to 100 times more effectively.[44-45] Thus petroleum jelly, a proved effective emollient, was used aiming at controlling the present dry skin status, enhancing effective drug absorption, and avoiding more irritation of the dry skin.

Moreover, little is available in the literature about the best treatment duration,[46] and as different studies cautioned against prolonged or intermittent use of fusidic acid for fear of resistance.[47] Thus the 3 weeks regimen for topical therapy of stage I seemed satisfactory, especially that the combined topical treatment included formulae that acted on the three factors often incriminated in the acne pathogenesis.

Oral antibiotics are the first-line therapy in patients with moderate to severe inflammatory acne[48] (the criteria of studied cases), this guided the choice of oral erythromycin 250mg tablets thrice daily for 3 months duration. The efficient results obtained without any side effects from topically or orally used antibiotics disagree with the study recommending that topical antibacterials should ideally not be combined with systemic antibacterial therapy for acne.[18]

Lastly, successful treatment of acne depends essentially on the degreasing of skin.[49] In addition, cleansing removes dead surface cells, preparing skin to better absorb topically applied medications.[50] Accordingly, the special acne soap was used before the application of topical medications.

Finally, although some reports assured that dietary restriction does not affect the treatment of acne,[3, 51-52] indication that diet may play a role comes from the studies by Bourne and Jacobs in 1956[53] and Cordain *et al*. in 2002.[9] Results of these studies inspired for diet control in this study strategy. The flaring up of acne lesions in one of the studied cases following chocolate and pickles intake, with rapid disappearance after strict diet control, is a good proof, although in one case, of the role of certain food material in acne management.

Stage II of this study started in each treated patient when all the visible inflammatory acne lesions disappeared. At that stage, the aim was to minimize as much as possible the residual post-acne scarring and to get rid of the troublesome postinflammatory hyperpigmentation. The choice of used formula was based on the following data.

Firstly, silver has a long and intriguing history as an antibiotic in human health care,[54] it reduces the inflammatory and granulation tissue phases of healing and enhances epidermal repair, with an uptake four-fold higher in damaged skin than in intact tissue.[55]

Secondly, salicylic acid has been used for many years for the treatment of acne,[3] it is effective against comedones and inflammatory lesions,[7,56] with fewer side effects.[6] It also induces controlled destruction or exfoliation of old skin and stimulation of new epidermal growth with more evenly distributed melanin. When it reaches the dermal layer, important wound-healing activities occur that cause skin remodeling and skin smoothening, both anti-aging benefits.[57] Superficial salicylic acid peels are cheap, safe and efficacious for treatment of acne vulgaris and with beneficial role in whitening the face of patients with acne and postinflammatory hyperpigmentation with minimal side effects.[6-7, 58-59]

Thirdly, useful treatment methods for acne include scrubs,[60] thus a daily facial scrubbing to remove continuously dead cells was recommended.

As patients were all females, so the last stage was concerned with naturally nourishing previously affected facial skin for cosmetic

purposes, naturally, because those patients have been subjected to intensive therapy with many chemical formulae known to affect the state of the skin especially facial one. Moreover, the beneficial effect of some natural products had stimulated their choice of use, aiming at trying to revitalize their facial skin to guard against recurrence of acne or any other skin infection, common to occur in those patients with atopic dermatitis. The choice was based on search in the Pubmed and Google of "natural remedies of acne". Accordingly, three naturally occurring elements i.e. yogurt, almond oil and honey were chosen and combined as a facial mask, that showed a satisfactory result.

Yogurt is an exceptional effective remedy for treating acne naturally, as it possesses numerous antibiotic-like properties, strengthens the immune system and kills bacteria within tiny hair follicles in addition to its ability to provide essential nutrients like vitamins and minerals to skin[61-62].

The sweet almond oil is known to be easily absorbed, leaving the skin soft and satiny smooth. Moreover, it doesn't clog the skin, thus doesn't leave it feeling greasy or tacky. It is ideal for chapped and irritated skin,[63-64] the case of studied cases.

Honey has been used long ago to treat wounds and cutaneous ulcers, and its healing properties have recently been rediscovered.[65] It debrides wounds rapidly, replacing sloughs with granulation tissue. Also its anti-inflammatory activity can be expected to prevent serous exudates, which can provide a medium for bacteria to colonize.[66] Honey is one of the best natural acne fighting ingredients. This is because honey actually kills *P. acnes*.[67-68]

Conclusion

Successful acne management necessitates the ability of the treating physician to apply therapy to the evolutionary stage of the disease and to target more than one of the pathogenic mechanisms and assuring careful planning of treatment regimens on individualized basis along with appropriate patient education, these all together frequently yields optimal responses.

As far as the author's knowledge, her work is the first of its kind, and may guide future studies towards management of those with acne *per se*, hoping that it may inspire other researches to find the best and successful treatment of this worldwide troublesome skin disease.

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