

Original Article

Combined topical therapy mixture can effectively and rapidly control atopic dermatitis lesions- a pilot study

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Abstract *Background* Topical steroids are the mainstay of therapy in atopic dermatitis. However, as massive colonization of lesional and non-lesional skin of atopic dermatitis patients with *Staphylococcus aureus* has been proved to exist and aggravate the skin lesions, thus topical antibiotics seem necessary to be added. New combined topical antibiotics and steroid formula eliminate forcefully the organism. Moreover, as topical medication penetrates a moist stratum corneum more effectively than it will penetrate a dehydrated stratum corneum, thus combining an emollient to atopic dermatitis therapy seems of utmost importance.

Objective To evaluate the effectiveness of combining two topical steroids, an antibiotic and an emollient as a single mixture in effectively controlling atopic dermatitis lesions in a six weeks treatment period.

Subjects and methods Thirty one females with atopic dermatitis were enrolled in this study. Disease severity was measured using the Severity Score of Atopic Dermatitis (SCORAD) index at baseline, 3 weeks and 6 weeks of therapy. They were treated with a mixture of mometasone furoate, fusidic acid and betamethasone valerate twice daily for six weeks.

Results Out of the 31 enrolled cases, 20 (64.5%) satisfied the inclusion criteria. They all completed the 6-week treatment regimen and evidenced no side effects from therapy. Statistical comparison between baseline and after three and six weeks interval using ANOVA and Tukey's multiple comparison tests revealed significant improvement of SCORAD index and its six clinical intensity signs with more effective improvement after the 6-week therapy. No correlation was ever detected by the Spearman test between index score and lesions' site or with allergic co-morbidities.

Conclusion The combined topical therapy mixture was effective and safe in rapidly controlling treated lesions.

Key words

Atopic dermatitis; combined therapy; emollient; topical antibiotics; topical steroids

Introduction

Atopic dermatitis (AD) remains a therapeutic challenge, and topical corticosteroids continue to have an important role. A large number of topical corticosteroids are available; they are

classified according to their potency into mild, moderate, potent or very potent.^{1,2}

In 1974, Leyden *et al.*³ stated that 90% of patients with atopic dermatitis have their skin colonized with *Staphylococcus aureus*. Thereafter, many studies evidenced increased carrier state of *S. aureus* in both involved and uninvolved skin of AD cases.⁴⁻⁸ Moreover, as *S. aureus* produces superantigens that proved to perpetuate the eczema,⁹ thus it was presumed that combining moderately potent topical corticosteroid and an antibiotic could

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tackle AD more effectively than steroids alone.¹⁰

Dry skin is a common skin condition as well as a key aspect of a number of diseases such as atopic dermatitis. It has a negative impact on the patient in terms of discomfort, pruritus and impaired quality of life. Within the overall treatment regimen for these diseases, the use of emollients to manage dry skin plays a considerable role in managing skin conditions,¹¹ to an extent that emollients are considered the mainstay of maintenance therapy for atopic dermatitis.¹²⁻¹⁴

Hence, the primary goal of this study was to evaluate the role of combining all the above mentioned medications together in a mixture and assessing its effectiveness in controlling AD lesions in six weeks. Thus, a moderately potent topical steroid cream, a topical antibiotic in a combined cream formula with another steroid in addition to an emollient were all mixed together to be used as twice daily topical therapy for six weeks.

Patients and methods

Study population

A total of thirty one patients with atopic dermatitis were recruited from "Allergy Unit" at Taif University. All the patients satisfied the diagnostic criteria of Hanifin and Rajka¹⁵ for atopic eczema. All patients provided their verbal consent and approval and were voluntarily included in this research study, which was performed in accordance with the Declaration of Helsinki (South Africa, 1996 amendment) and Good Clinical Practice guideline.

Patients were ineligible for the study if they had periorbital and/or facial eczema (four cases) or extensively generalized eczema (seven cases) for fear of side effects from the use of two topical steroids on delicate skin or

on a large body surface area. Thus a total of 20 cases were actually enrolled in this study, (age range, 19-26 years; mean age 22.9 ± 2.532 years). It is worth mentioning that unintentionally those who satisfied the inclusion criteria and agreed to participate in this study were all females.

Assessments

Six clinical signs were recorded for each case by the senior consultant in the Unit for practical purposes: erythema, edema/papulation, oozing/crusting, excoriations, lichenification and dryness. These clinical signs are the most widely used and validated in atopic dermatitis currently available scoring system: Scoring of Atopic Dermatitis (SCORAD) index,¹⁶ The SCORAD scored the extent, six intensity criteria, and subjective symptoms of AD. Disease extent was measured using the rule of nines. The average intensity of each clinical sign was graded on a scale from 0 to 3 (0=absent, 1=mild, 2=moderate, and 3=severe) at a representative body site, per the SCORAD protocol. Subjective symptoms, pruritus, and sleep loss were evaluated with regard to the last 3 days and nights, and all were scored by the patients. Both subjective items were graded on a 10-cm visual analogue scale. The SCORAD index formula is: $A/5 + 7B/2 + C$. In this formula A is defined as the extent (0-100), B is defined as the intensity (0-18) and C is defined as the subjective symptoms (0-20). The maximum SCORAD score is 103 (i.e. patients with high score are rated "worse").

Mometasone furoate 0.1% cream (Elocom® cream) and fusidic acid 2% combined with betamethasone valerate 0.1% cream (Fusibact-B cream®) were mixed by the patient in a glass jar with petroleum jelly (50ml) (Vaseline®). Mixture was applied on the lesions twice daily, and for hand and feet eczema, cotton gloves and socks was recommended to be worn respectively to avoid

loss of applied drug while walking or using hands.

Participant flow and follow up

A detailed history with SCORAD assessment was performed at the first visit (baseline). All patients who met eligibility criteria started twice daily topical therapy application. Participants had clinical re-assessments at week 3 and week 6 by the senior consultant in the Unit. The primary outcome measure was effective and rapid control of eczematous lesions, evidenced by decrease in the SCORAD index score. As this was met in all studied cases, thus compliance was satisfactory. After the six week, patients continued on daily emollient use alone.

Data analysis

Statistical analyses were done using a software program (SPSS for Windows version 15.0; SPSS Inc, Chicago, IL). The mean patient-SCORAD index severity score was calculated and compared using the "Repeated Measures ANOVA test". The Tukey's multiple comparison test was used to determine which means amongst the studied set of means differ from the rest, as the ANOVA lead to a conclusion that there is evidence that the group means differed. Spearman's rank correlation coefficient was used to detect any correlation between the index score, the allergic co-morbidities and eczema site(s). Statistical significance was defined as a p value <0.05 for Tukey's multiple comparison and Spearman's rank correlation coefficient tests and as $p < 0.001$ for ANOVA test.

Results

Study population

In total, 31 patients were assessed for eligibility to participate in this study; of these, 20 female patients with an age range of 19-26 years (mean age 22.9 ± 2.532 years) were enrolled and received the twice daily topical

combined therapy. At baseline, all except one patient were classified as severe AD cases (SCORAD >40), thus severity grouping could not be performed. Assessment of prevalence of other allergic co-morbidities in the studied population, evidenced asthma in 10 cases(50%), allergic rhinitis in 19 cases(95%), urticaria in 16 cases(80%), with food allergy and latex allergy in 8 (40%) and 2 (10%) cases, respectively.

Responsiveness

The 20 enrolled cases all completed the planned 6-week treatment study period, with no reported local side effects. **Table 1** shows the significant improvement in the SCORAD index score and its six clinical intensity signs after three and six weeks of treatment. However, as the ANOVA test used in this table evidenced group means difference, but did not determine at which period precisely improvement was more evident, thus the Tukey's multiple comparison test was used to clarify this dilemma. This table shows significant difference between means at the three treatment milestones, indicating that the combined treatment was effective both after three and six week's period but it was more effective after six weeks of therapy.

Spearman rank coefficient correlations between the baseline SCORAD index score and each of the reported allergic co-morbidities ranged from -0.165 for bronchial asthma to -0.378 to allergic rhinitis and allergic conjunctivitis. For each of the studied item, no correlation could be detected ($p > 0.05$). Similarly, no correlation could ever be detected between the baseline SCORAD index score and site of AD lesions.

Discussion

Topical corticosteroids have been the mainstay of treatment for AD over the past 40 years.¹⁷ Currently, there is no standard therapeutic

Table 1 Tukey's Multiple Comparison Test of SCORAD index and its clinical intensity criteria at baseline, after 3 and 6 weeks of therapy.

	<i>Mean difference</i>	<i>q</i>	<i>95% CI of difference</i>	<i>P value</i>
SCORAD index				
A	22.52	40	20.58 to 24.46	< 0.05
B	38.02	67.53	36.07 to 39.96	< 0.05
C	15.50	27.53	13.55 to 17.44	< 0.05
Erythema				
A	1.650	19.28	1.355 to 1.945	< 0.05
B	2.450	28.63	2.155 to 2.745	< 0.05
C	0.8000	9.348	0.5047 to 1.095	< 0.05
Edema/papule				
A	1.100	15.42	0.8539 to 1.346	< 0.05
B	1.600	22.43	1.354 to 1.846	< 0.05
C	0.5000	7.010	0.2539 to 0.7461	< 0.05
Oozing/crust				
A	0.5500	5.772	0.2212 to 0.8788	< 0.05
B	0.9500	9.970	0.6212 to 1.279	< 0.05
C	0.4000	4.198	0.07120 to 0.7288	< 0.05
Excoriation				
A	1.000	25.17	0.8629 to 1.137	< 0.05
B	1.900	47.82	1.763 to 2.037	< 0.05
C	0.9000	22.65	0.7629 to 1.037	< 0.05
Lichenification				
A	0.4500	5.604	0.1729 to 0.7271	< 0.05
B	1.400	17.44	1.123 to 1.677	< 0.05
C	0.9500	11.83	0.6729 to 1.227	< 0.05
Dryness				
A	0.8000	12.59	0.5808 to 1.019	< 0.05
B	1.700	26.76	1.481 to 1.919	< 0.05
C	0.9000	14.17	0.6808 to 1.119	< 0.05

a= Baseline versus after 3 weeks therapy, b= baseline versus after 6 weeks therapy, c= after 3 weeks versus after 6 weeks therapy

regimen for the long-term management of moderate to severe atopic dermatitis but most regimens include a topical steroid and an emollient.¹⁸ Topical applications containing corticosteroid compounds vary greatly in potency. In general the more potent ones are associated with the greater risk of adverse effects.¹⁹

Mometasone furoate; is a highly effective topical corticosteroid with a less systemic absorption and a low potential for local and systemic side effects.^{20,21} Once-daily use of mometasone furoate was found to result in a greater percentage improvement in total atopic

dermatitis scores compared with twice-daily betamethasone valerate in one study,²² and an improvement in pruritus only in another study compared with twice-daily hydrocortisone 17-butyrate.²³

The frequency of application is a key clinical issue when prescribing topical corticosteroids. Topical corticosteroids are available for application one to four times per day. Although there are few empirical data to assess the patterns of prescribing with respect to frequency of application, it is generally accepted that a twice-daily regimen is the most

widespread approach to the use of topical corticosteroids in atopic eczema.²⁰

Guidelines from the British Association of Dermatologists suggest that the use of topical corticosteroids should be limited to a few days to a week for acute eczema and for periods of up to 4–6 weeks to gain initial remission for chronic eczema.²⁴

S. aureus has a peculiar ability to colonize the skin of patients with eczema and AD and is consistently found in eczematous skin lesions in these patients. The skin lesions of 80-100% of patients with eczema and AD are colonized with *S. aureus*. In contrast, *S. aureus* can be isolated from the skin of only 5-30% of normal individuals, mainly from intertriginous areas.^{8,25,26} A correlation between the severity of the eczema and colonization with *S. aureus* has been demonstrated, and it has been determined that bacterial colonization is an important mechanism aggravating skin lesions.^{26,27,28} Hence the eradication of *S. aureus* may lead to a steroid-saving effect.^{25,29,30} Moreover, aside from an anti-inflammatory effect, treatment with topical steroids contributes to a reduction of skin colonization with *S. aureus* and therefore might affect a further trigger of AD.^{31,32} Therefore, a combination topical treatment with antibacterial and corticosteroid agents has been recommended.³³⁻³⁶

Topical fusidic acid proved to reduce the prevalence and population density of *S. aureus* without increasing fusidic acid-resistant *S. aureus*.³⁷ Moreover, the new combined fusidic acid-betamethasone lipid formulation showed more strength in eliminating bacteria originally present in these skin lesions,³⁸ and relieved the dryness of atopic dermatitis skin.³⁹

Therapies directed towards restoring the impaired barrier function of the epidermis seem to be of significant importance in AD.

Emollients, which reconstruct integrity and continuity of stratum corneum, may blockade penetration of air-borne allergens across damaged skin barrier and prevent AD flares.⁴⁰ Studies proved that combined steroids with emollients could reduce the total high potency topical corticosteroid consumption, resulted in significantly greater improvement of disease severity, pruritus and skin dryness compared to corticosteroid treatment alone, decreased the risk of irritant contact dermatitis in AD and significantly improved skin dryness and enabled to maintain the achieved remission in the majority of patients.⁴¹⁻⁴⁴

In this study and based on the fore mentioned data, emerged the idea of combining all these drugs together to effectively control AD lesions in a six weeks twice daily treatment regimen. This guarded against the hazards of prolonged use of topical steroids; the mainstay of therapy in AD; and the emergence of resistant *S. aureus* strains.

However, there were limitations to this study; Firstly: no control group was included, this could be explained by the fact that the efficacy of these medications separately or in two combined formula have been extensively studied and all our patients had used at one time during their disease course, and so they did not accept to re-use. Secondly, no swab was taken from the treated lesions to affirm presence of *S. aureus* and to correlate between the severity of the eczema and colonization. However, in accordance with the succinct remark of Leyden *et al.*³ assuring that 90% of patients with atopic dermatitis have their skin colonized with *S. aureus*, topical antibiotic was added.

Strength of this study was the fact that although the quality of life indices were not studied, but the great improvement in patients' clinical status was a good solid proof of their improvement.

On Summary, the twice daily combined topical therapy mixture had effectively and rapidly controlled non-facial and non-extensive atopic eczema, during a short treatment period (6 weeks) and thus minimizing possible side effects.

Acknowledgement

I would like to thank all those who had helped in the establishment of the "Allergy Unit" in Taif University, first Unit in all Saudian Universities.

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