Clinical evaluation of an herbal, topical cream in the treatment of eczema: A double-blind, randomized, placebo controlled study.

Mark J. McNamara, BA, Steven R. Frank, BS, Breeana K. Saffell, BA, & Gary Clark MD

3125 Sterling Cir. Ste 101
Boulder, CO 80301

Abstract

Introduction- Eczema, an inflammatory condition of the skin, affects over 15 million Americans a year. Standard medical care includes the use of topical steroidal creams, avoidance of known allergens, and the administration of immuno-modulators in severe cases. The present study examines the safety and efficacy of a topical, herbal, cream for the relief of mild to moderate eczema. The product, Nature's Rite Rash Relief, has shown notable anecdotal results during the period of field trials and through product introduction.

Methods- Subjects were consented, enrolled, and followed for a total of 4 weeks. During weeks 2 and 3, subjects applied either the investigational product (IP) or a placebo three times a day. Subjects recorded on a daily basis the severity of sleep interference, itching, pain, overall discomfort, redness, crusting, overall appearance, and interference with daily activities.

Results- 18 subjects completed the trial and were included in the analysis. The mean symptom rating in the baseline week for the control group and the test group were 3.50 and 3.58 respectively. The mean change in symptoms between week 1 and week 3 were –0.14 for the placebo group and –0.70 for the test group. This difference was significant ($p<0.01$). There were no adverse effects noted in the study.

Discussion- The present study demonstrates the clear superiority of the IP over placebo when used to relieve symptoms associated with eczema. The product is safe to use intermittently or as a maintenance treatment. Although the study allowed for only 2 weeks of product application, this is a condition that often requires longer periods of time to clear fully. The subjects in the study showed clear benefit from the use of the IP and follow-up observations of those in the study illustrated continued improvement.

Introduction

Eczema is a general term for a variety of chronic inflammatory conditions of the skin. Eczematous skin often presents as a localized rash of itchy, red, dry, and scaly areas. Though poorly understood, the cause of eczema seems to be closely linked to heredity, and sensitization to one or many allergens. The mechanism behind the skin inflammation is an immune reaction that causes an increase in inflammatory cytokines. The condition is most often contracted in childhood, and diagnoses of asthma and hay fever often follow later in life [9]. Though eczema is not traditionally thought of as a severe condition, the societal burden it creates is significant. Estimates show more than 15 million Americans are affected with eczema of one form or another, and payments from insurance companies to cover the costs of their patients with eczema amount to over 1 billion dollars per year [4].

In the course of treatment, clinicians will often discuss allergen exposure, and how to rule out various external allergens that may be exacerbating the condition. Lotions and emollients help to keep the skin hydrated and free of xeroses and may reduce the need for corticosteroids, but once an outbreak has begun, these topicals are often of little use. The medical standard of care most often recommended for eczema consists of topical corticosteroids used in short bursts to suppress symptoms while avoiding long-term use. This is due to the fact that long-term use of topical corticosteroids has been associated with skin atrophy, striae, and development of tolerance [9]. Two new treatments, topical tacrolimus and picrolimus, have recently been approved for use on eczema, but the long-term effects of its use are unclear. Several studies have discovered an increased prevalence of skin cancer in animals treated with the compounds [1]. Presently, no treatment for eczema that has been deemed efficacious at suppressing outbreaks has been approved for long-term use without the possibility of side effects [9].

The present study was undertaken to determine the safety and efficacy of the investigational product (IP), a topically applied herbal cream, in promoting healing and relieving symptoms associated with eczema. The cream contains herbs with anti-inflammatory, antiviral, anti-fungal, analgesic, and tissue-regenerating properties [5].

Materials & Methods

After giving written consent, twenty-two subjects were enrolled in this double-blind, placebo controlled trial, and randomized to receive either the IP or a placebo cream. Subjects were seen once a week for four weeks (total of 5 visits). Each weekly visit consisted of a verbal interview, a symptoms survey filled out in the presence of the clinician, and a photograph of the treatment area. Subjects filled out a daily symptoms survey once a day at home for the duration of the trial. Symptoms surveys asked the subject to rate the severity of their symptoms on a scale from 1 to 9. A rating of 1 was defined as “none at all”, and a rating of 9 was defined as “as bad as it could be”. Symptoms assessed by the symptoms survey form are detailed in Table 1.

Subjects were instructed to refrain from the use of any oral antihistamines, or corticosteroids. Though topical corticosteroid, and emollient use was prohibited in the treatment area, the use of an unmedicated moisturizing lotion (Cetaphil and Eucerin) was

allowed. The first week was designated as a baseline week to assess each subject's symptoms when free of treatment. The second and third week were designated as treatment weeks, during which the subjects were instructed to apply the assigned cream three times a day while continuing to fill out their surveys. Subjects were given tubs of cream labeled only with their number. Subjects were instructed to saturate the treatment area with the cream at each application. The last week was designated as a return to baseline week as a means of determining any lasting effects of the IP.

Statistical analysis was performed using Microsoft excel. T-tests (two tailed) were used to determine the difference between the test and control groups (alpha=0.05).

Table 1- Symptoms tracked by patient surveys

Symptom	Described to the subject as:
-Severity of sleep interference	Difficulty in getting to sleep or staying asleep through the night.
-Severity of itching	Degree to which you find yourself wanting to scratch your rash.
-Severity of pain	Degree of pain from damage to the skin.
-Severity of overall discomfort	Degree of overall physical discomfort including itching and pain.
-Severity of redness	Degree to which eczema is inflamed compared to unaffected areas.
-Severity of crusting	Degree of dryness and flaking of dry, dead skin.
-Severity of overall appearance	Degree of overall physical appearance including redness and crusting.
-Severity of daily interference	Degree to which eczema symptoms interfered with any daily activities.

Results

Subjects enrolled were aged 19-84 (mean, 42.5). Of the 22 subjects enrolled (5 male, 17 female) and consented into the study, 19 subjects completed the trial course. A total of 18 subjects, 9 test subjects and 9 control subjects, were included in the analysis. A subject in the test group was dismissed from the study for failure to fill out symptom surveys reliably at home. A subject in the placebo group was dismissed from the study after it was discovered she had been using an oral antihistamine as needed for an unrelated sinus issue. Another subject in the placebo group dropped out of the study due to a flare in their condition. The stated reason for leaving was that they did not wish to refrain from using hydrocortisone for the duration of the trial. Another subject's data was excluded from the test group data set when it was determined that psychological stress experienced by her during the duration of the trial was uncharacteristic of her life, making it difficult to differentiate changes in symptoms reflecting stress and those reflecting a natural progression of the disease.

The mean symptom rating in the baseline week for the control group and the test group were 3.50 and 3.58 respectively. The mean symptom rating in the second week of treatment (week 3) was 3.30 for the control group and 2.92 for the test group a change of –0.20 and –0.66 respectively, though this was not statistically significant. The average changes from week 1 to week 3 in symptom scores are reported for both control and test groups in Figure 1.

The mean change in symptoms between week 1 and week 3 (Figure 1) were –0.14 for the placebo group and –0.70 for the test group ($p<0.01$). Similarly, the average changes in symptom severity between weeks 2 and 3 (Figure 2) reached significance with the placebo group's average rating rising by 0.34 and the test group's average rating falling by 0.17 ($p<0.001$). The test group also experienced a significant drop (-0.12) over the placebo group (-0.0034) from week 2 to week 4 ($p<0.05$) (Figure 3). Subjects in the test group experienced a near significant ($p<0.07$) reduction in the severity of crusting from week 2 to week 3. Subjects in the test group experienced an average reduction of 0.33 in the severity of crusting, while the placebo group's severity increased by an average of 0.40. Of interest is also the difference between groups in the change in severity of symptoms from week 3 to week 4; this is the return to baseline period. The placebo group's symptoms actually decreased in severity by an average of 0.38 while the test group's symptoms rose by an average of 0.05 ($p<0.001$). The significant differences found between groups between different weeks are summarized in Table 2.

No serious adverse events were recorded in either the control or placebo group, and side effects reported were limited to reports of mild tingling after application of the gel. These reports were similarly distributed between the control and test groups.

Table 2. Findings reaching significance.

Parameter	Placebo	Test	P<
Difference in crusting from week 2 to week 3	**0.40**	**-0.33**	**.07**
Difference in severity of symptoms from week 1 to week 3	**-0.14**	**-0.70**	**.002**
Difference in severity of symptoms from week 2 to week 3	**0.34**	**-0.17**	**0.000006**
Difference in severity of symptoms from week 2 to week 4	**-0.0034**	**-0.12**	**0.02**
Difference in severity of symptoms from week 3 to week 4	**-0.38**	**0.05**	**0.0000005**

Figure 1- Change in severity of symptoms from week 1-3

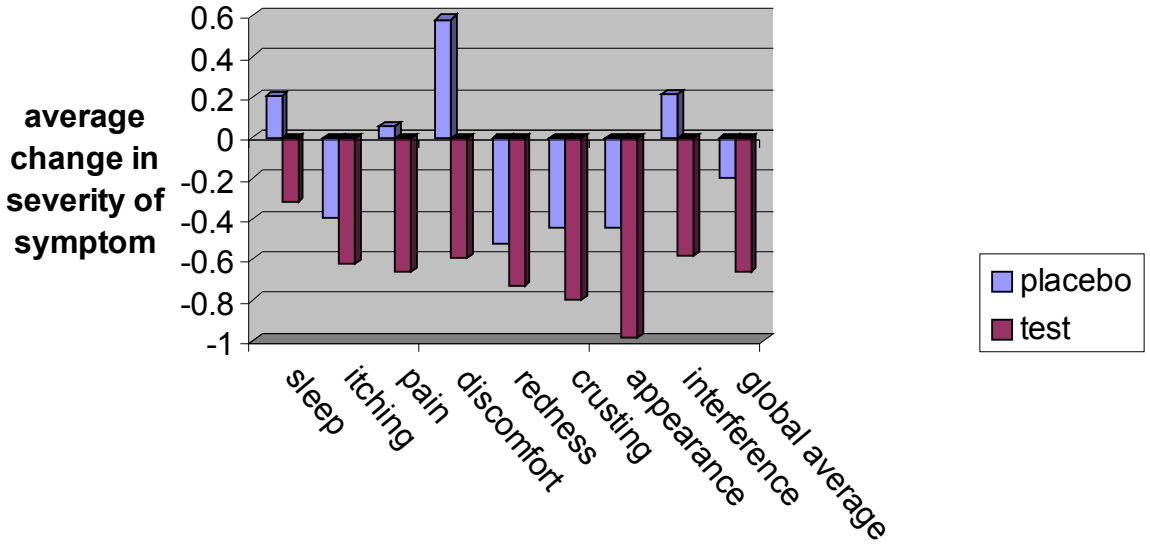


Figure 2- Change in severity of symptoms from week 2-3

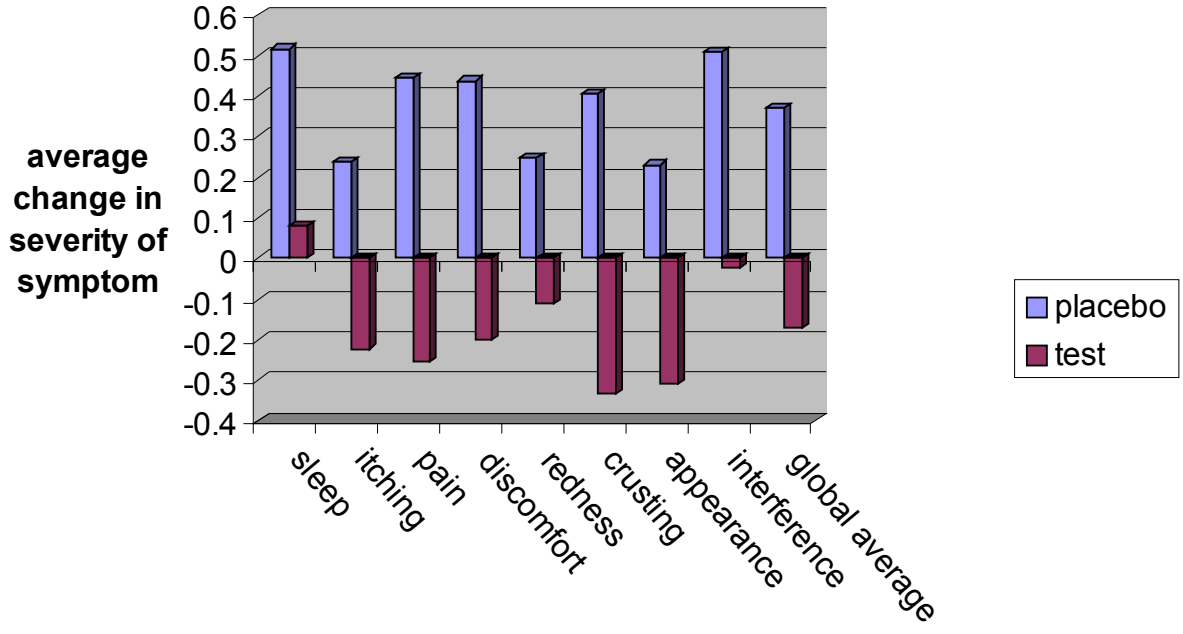
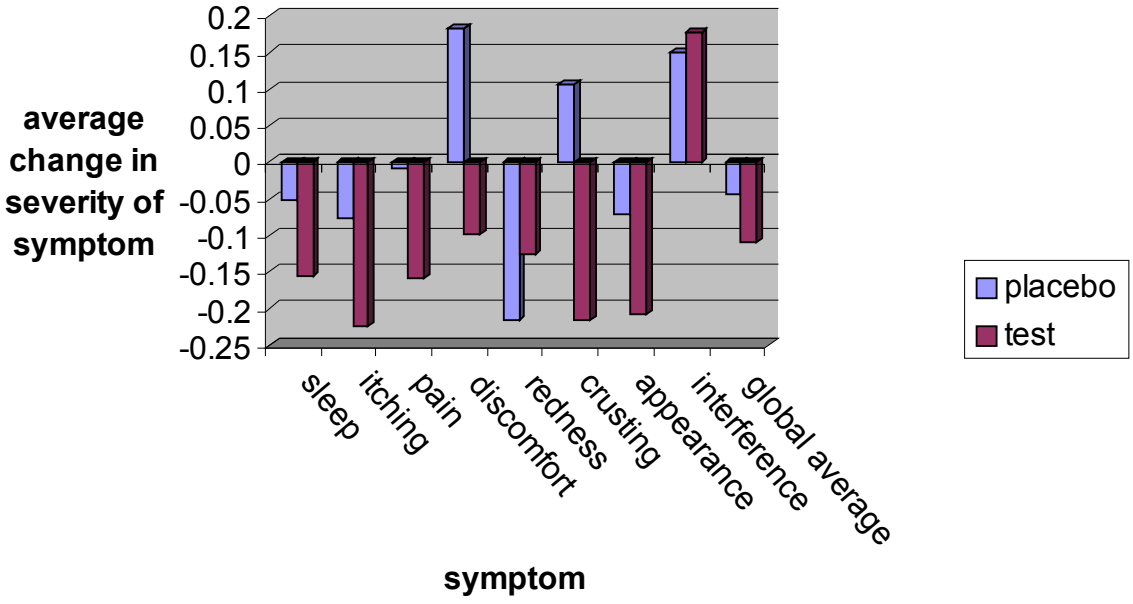


Figure 3- Change in severity of symptoms from week 2-4



Discussion

The pathophysiology of eczema is poorly understood, at best. In addition, little reliable, scientifically based research exists exploring the physiological actions exerted by the herbs used in the IP [6]. These two facts make drawing conclusions regarding the mechanisms behind the therapeutic actions of the IP difficult.

The herbs in the cream are designed to perform several functions. The first of these is as an antimicrobial to prevent infection in the area [5]. Secondary bacterial infections of the eczematous area release enterotoxins that feed the inflammation cycle by inciting the production of IgE antibodies, and activation of T-cells [2, 7, 8].

An additional feature of the herbs is to directly quell the inflammation and nerve irritation to provide relief to the patient. This is accomplished with anti-inflammatory and analgesic herbs. These herbs help to break the inflammation cycle by soothing irritated nerves.

The herbal constituents are delivered topically in an aloe vera based gel with essential oils to make it a cream. The oils provide an excellent source of essential fatty acids and vitamins A and E, while vitamin C is added to adjust pH and assist in healing. A cell

proliferating herb is included to increase the rate at which new skin can be formed to maintain the integrity of the skin, and prevent continued vulnerability to bacteria and fungus [5].

It is important to consider that the entire duration of the test period was 4 weeks. The first and last weeks were baselines, leaving only a two-week application period. When this is coupled with the small size of the study (n=18) the fact that clinical efficacy was demonstrated with statistical efficacy is truly impressive. As this was a small pilot study to evaluate the test protocol and establish whether there was sufficient evidence to warrant a full clinical study, the results are clearly positive.

The results of the current study illustrate the clear benefit of the IP over placebo after only two weeks of treatment. The demonstrated safety profile of the IP, and the lack of steroid compounds in the treatment, makes it an attractive option to chronic sufferers of eczema. Often these individuals are forced to settle for repeated courses of topical steroid use to calm flares. Not only can the IP be used to calm eczema outbreaks, but also due to its benign nature it can be used as a maintenance treatment to maintain healthy skin without risk of skin atrophy.

Due to the strong healing effect of some of the cream constituents, the cream seems to offer the opportunity for prolonged use to allow for continued improvement. This ability to maintain treatment would be a clear benefit over topical corticosteroid preparations, which are approved for only short-term use. A long-term study will indicate whether continued use will allow complete remission.

References:

1. "Alert for Healthcare Professionals: Pimecrolimus (marketed as Elidel)." U.S. Food and Drug Administration: Center for Drug Evaluation and Research. March 2005. U.S. Food and Drug Administration. 29 Jul. 2005 <http://www.fda.gov/cder/drug/InfoSheets/HCP/elidelHCP.html>.
2. Behrendt, H., Ring, J. (1990). Histamine, antihistamines and atopic eczema. Clin Exp Allergy 20(supp 4): 25-30.
3. Bluefarb, S.M. (1972). Clinical comparison of Desonide cream with Betamethasone Valerate cream: a double-blind randomized study. Int J Dermatol 11: 73-76.
4. "Handout on Health: Atopic Dermatitis (A type of eczema)." National Institute of Arthritis and Musculoskeletal and Skin Diseases. April 2003. National Institutes of Health Department of Health and Human Services. 29 June 2005 <http://www.niams.nih.gov/hi/topics/dermatitis/AtopicDerm.pdf>.
5. PDR for Herbal Medicines. 2nd ed. Flemming, Thomas Ed. Montvale: Medical Economics Company, 2000.
6. Ruzicka, T. (1998). Atopic eczema between rationality and irrationality. Arch Dermatol 134: 1462-9.
7. Strange, P., Skov, L., Lisby, S., Nielsen L. P., & Baadsgaard, O. (1996). Staphylococcal enterotoxins B applied on intact normal and intact atopic skin induces dermatitis. Arch Dermatol 132: 27-33.
8. Wehner, J., & Neuber, K. (2001). Staphylococcus aureus enterotoxins induce histamine and leukotriene release in patients with atopic eczema. Brit J Dermatol 145: 302-5.
9. Williams, H. C. (2005). Atopic dermatitis. N Engl J Med 352: 2314-24.