Original Article

Comparison between two moisturizing lotions with different pHs in skin moisture improvement and pruritus reduction

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ABSTRACT

Introduction: Atopic dermatitis (AD) affects approximately 15% of the population and is one of chronic inflammatory diseases more common in childhood. Intense pruritus and skin xerosis are the most important symptoms of the disease. Restoration of epidermal barrier protection elements through the use of emollients is essential for disease treatment. **Objective:** To evaluate the improvement in pruritus, skin hydration, and xerosis in two groups of patients using the same moisturizer (colloidal oatmeal, glycerol and petrolatum), but with different pH values in patients with AD. **Method:** Twenty-one patients aged 7 to 54 years with AD and moderate to severe pruritus were randomly divided in two groups. The groups were switched after 30 days. **Results:** The results were assessed after 60 days. Improvement in pruritus, xerosis, and hydration were evaluated by the physician, the patient, and by corneometry. There was no statistical difference in the two groups; therefore, data were evaluated as belonging to a single group at the end. Decrease in pruritus was observed by 59% of patients and 52% of physicians; xerosis reduction was observed by 52% of patients and 43% of physicians. The level of skin hydration in areas with eczema has increased by 79% compared with baseline period. **Conclusion:** Moisturizers containing colloidal oatmeal, glycerin, and petrolatum with pH close to the one in normal skin showed to be appropriate to improve pruritus in patients with AD.

Keywords: atopic dermatitis, pruritus, xerosis, moisturizer.

INTRODUCTION

Atopic dermatitis (AD) affects approximately 15% of the population and is the most common chronic inflammatory dermatosis in childhood.[1,2] Half of the cases begin in the first year of life and its clinical manifestations usually improve with age.[1,2] Because it is a dermatosis in which pruritus is the predominant symptom, it has great physical and psychological impact on patients and their families.[1,2] The effectiveness of current conventional treatments (antihistamines) for pruritus is limited and although new drugs such as cyclosporine and macrolides appear promising for its control, this symptom is still a great therapy challenge.[1,2]

Pruritus is usually of a variable intensity throughout the day, worsening at night and leading to scratching, which will produce many of the stigmas of AD such as pruritus, lichenification, onset and persistence of eczema. It is one of the main responsible for reducing sleep quality and causing mood disorders, with impact on patients' quality of life,[3,4,5,6] being one of the important criteria for AD diagnosis according to Hanifin and Rajka.[7,8,9] Criteria described by these authors in 1980 are now the most widely used in scientific research because they are more comprehensive.[6] The diagnosis is exclusively clinical and the main criteria used are: presence of pruritus, involvement of face and flexural areas in children and infants, flexural lichenification in adults, chronic or recurrent dermatitis, and personal or family history of atopic disease.[6,7,8,9]

Chronic pruritus has a multifactorial etiology and is triggered by stimulation of free nerve endings at dermoepidermal junction.[10,11] Both painful and pruritogenic stimuli are transmitted by type C nerve fibers to the thalamus. Skin of patients with AD shows a tendency to start and prolong the duration of pruritus triggered by minimum factors due to a reduction in the excitability threshold of these fibers when compared to normal skin.[10]

Many pruritus triggering factors in atopic individuals are known, among them the skin xerosis, a reflection of disturbance in the barrier by increased transepidermal water loss and reduced capacity of stratum corneum to retain water.[5,9] This change facilitates the entry of other irritant and itchy agents, worsening pruritus condition.[10] Thus, the use of emollient creams to keep skin moisture produces a film that limits water evaporation, restoring the barrier function lost before by the skin and, therefore, reducing pruritus.[6,12]

Moisturizers with low pH can be especially useful in recovering the skin barrier function, since this site proximity to the physiological acidic pH results in a rapid improvement and maintenance of skin properties.[13] Therefore, these moisturizes are believed to cause fewer side effects such as burning and discomfort on use.[13]

This original study aims to assess whether there are differences between two emollients of identical composition (colloidal oatmeal, glycerin and petrolatum), but with two different pH values close to normal skin pH (4.5, 6.5), one with pH 5.3 and another with pH 6.3, for skin hydration of patients with atopic dermatitis, in the improvement of pruritus, skin hydration, and reduction in areas of eczema,. Clinical evaluation was performed by a physician, subjective evaluation by the patient, and objective study by corneometry.

MATERIAL AND METHODS

This was an exploratory, double-blind, randomized, and monocentric study with total duration of 75 days. The objective was to evaluate the improvement of pruritus, skin hydration, and reduction in areas of eczema in two groups of patients using two emollients with exactly the same composition (colloidal oatmeal, glycerin and petrolatum), but with different pH values, one at pH 5.3 and another at pH 6.3.

Subjects were patients with atopic dermatitis, registered in the outpatient Dermatology Department of PUC Campinas University Hospital. They were approached by telephone by the researcher and, after informed of all the necessary information, patients were invited to participate in the study as volunteers, and an outpatient visit was scheduled. Informed consent was obtained before performing any procedures related to the study and after subjects have received sufficient information about the study and had their questions answered.

This protocol and all accompanying materials delivered to patient were submitted by the investigator to the approval of the Research Ethics Committee (REC). Approval of REC was obtained before the start of the study and documented in a letter to the researcher, clearly identifying the trial, documents reviewed, and date of approval. A list of members participating in the meeting must be present, including the functions of those members. If members of the study team are not present, it should be clear that they did not vote.

Inclusion criteria were age between 7 and 54 years, diagnostic of atopic dermatitis of mild to moderate degree according to Hanifin and Raika criteria, and presence of any degree of pruritus. Were excluded the patients treated with systemic steroids, phototherapy, cyclosporine, macrolide antibiotics or those who have had ended any of these treatments less than 30 days prior to the study. Also were excluded patients with a medical history of one of the following diseases: diabetes mellitus, chronic renal failure, cholestasis, hypothyroidism, hyperthyroidism, Human Immunodeficiency Virus (HIV), and chronic hepatitis or any disease that the investigator deems to interfere in the study conduct and/or analysis of clinical data; patients in the pregnancy period or nursing; patients participating in another clinical study or who have completed a clinical study during the 4 weeks prior the beginning of this study; patients considered by the investigator as unable to complete the study; patients taking systemic retinoids or who have ended treatment less than 3 months prior to the study, systemic antihistamine other than hydroxyzine (maximum dose of 25 mg/day for 2 consecutive days or 3 days interspersed, during the interval of 15 days, in any period of the study), systemic non-macrolide antibiotic for any purpose for more than 10 consecutive days during the study.

A total of 36 volunteers (male and female) with AD were selected to participate in the study, aged between 7 and 54 years. Patients were instructed to restrain the use of any moisturizer product for dermatitis treatment during 15 days. After this period, they were randomized into two groups, one with lotion at pH 5.3 and the other at pH 6.3 for 30 days. After this 30 days period, the groups were switched.

The intensity of pruritus and xerosis were clinically evaluated before treatment (visit 1); after 15 days using the moisturizer, considered the baseline of the study (visit 2); and every 15 days of treatment, totalizing 60 days of study (visits 3, 4 and 5).

A questionnaire was administered to volunteers for self-evaluation during treatment. Tolerability was assessed by the presence of irritation, worsening of pruritus, clinical worsening and its relationship to medication. These symptoms were recorded in the same questionnaire every day by

volunteers. Instrumental measures such as imaging system and corneometer were taken for assessment of hydration levels and quality of skin's appearance at baseline (visit 2) and every 15 days of treatment (visits 3, 4 and 5).

RESULTS

Of the 36 selected volunteers, 20 completed the study. Nine volunteers discontinuated the study, 7 volunteers were excluded from the study and the reasons are listed below in Table 1.

Statistical analysis indicated that there was no significant difference between treatments with lotions at pH 5.3 and pH 6.3. Therefore, data from both groups were assessed as a single treatment with a total of 60 days.

According to medical evaluation, there was an improvement in xerosis condition in 43.48% of the volunteers, and 52.17% remained stable (Figure 1). Regarding pruritus, there was an improvement in 52.17% of the volunteers, and 39.13% remained stable (Figure 2). Volunteers evaluation showed an improvement in xerosis condition in 52.27% of cases, and 40.91% remained stable (Figure 3). Pruritus improved in 59.09% of the cases, while 31.82% remained stable (Figure 4). Objective evaluation was performed by corneometry, which provides information on the level of hydration in the outer layer of skin, called stratum corneum.

After 60 days of treatment, there was a 79% increase in hydration level of regions with eczema. Comparison was made between baseline measurement performed before the use of products and final measurement performed after 60 days of products use (Figure 5). After 30 days of treatment with the products, the level of moisture in areas of skin with eczema equaled the level of hydration in regions without eczema (Figure 6). There was also a visible decrease of xerosis and desquamation during treatment and more markedly at the end of treatment; 60 days of moisturizer use (Figure 7).

Tabela I – Reason for protocol discontinuation

Volunteer	
n° 6	Use of prohibited medication for the study (dexchlorpheniramine) in V3
n° 21	Use of prohibited medication for the study (amoxicillin) in V2
n° 22	Use of prohibited medication for the study (amoxicillin) in V2
n° 23	Use of prohibited medication for the study (amoxicillin) in V5
n° 35	Use of medication allowed, but for longer than allowed (dexchlorpheniramine maleate) in V5
n° 37	Use of prohibited medication for the study (dexchlorpheniramine) in V5
n° 38	Use of prohibited medication for the study (prednisone) in V4

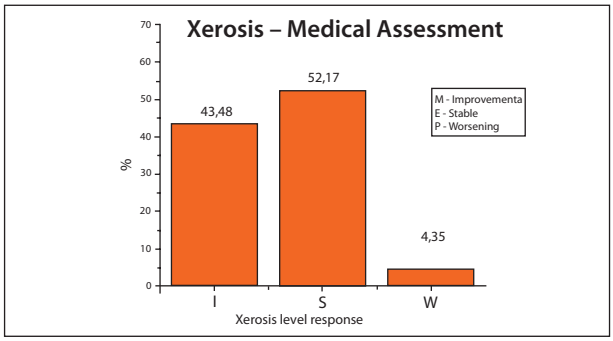

Figure 1 – Medical assessment of xerosis level.

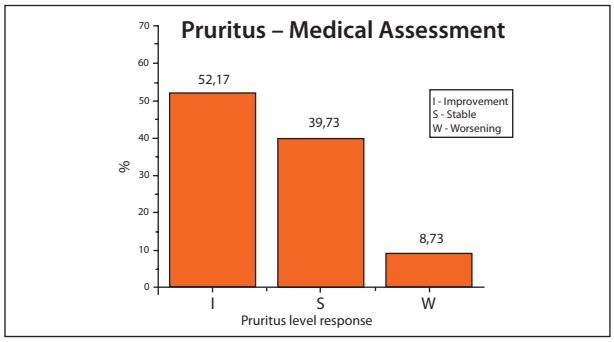

Figure 2 – Medical assessment of pruritus level.

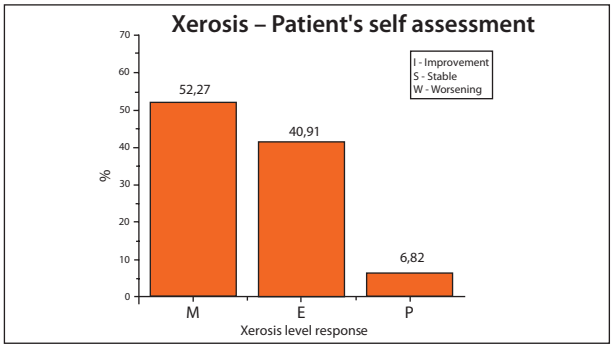

Figure 3 – Patient's self assessment of xerosis level.

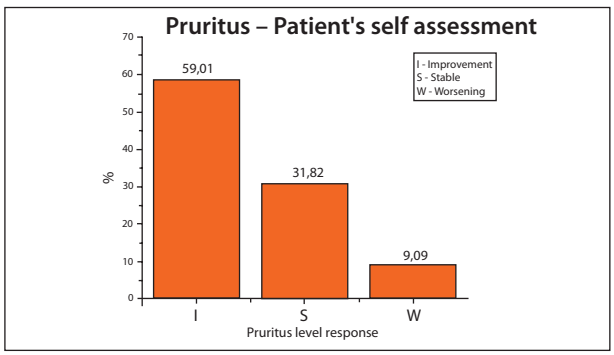

Figure 4 – Patient's self assessment of pruritus level

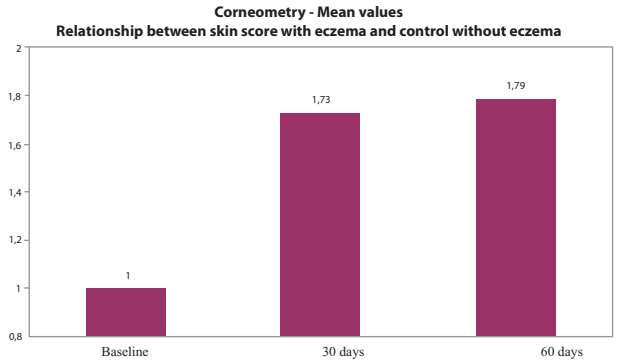

Figure 5 – Level of skin hydration after treatment.

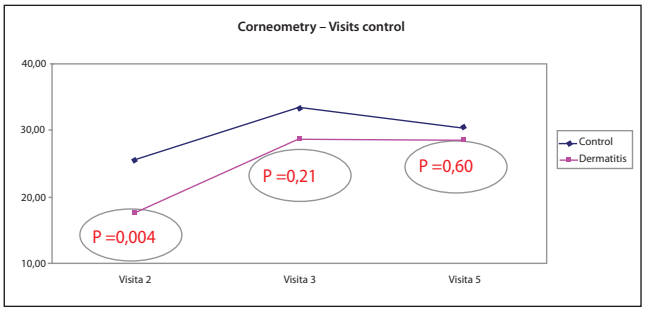

Figure 6 – Level of skin hydration after treatment. Comparison between the area with eczema and the area without eczema (control).

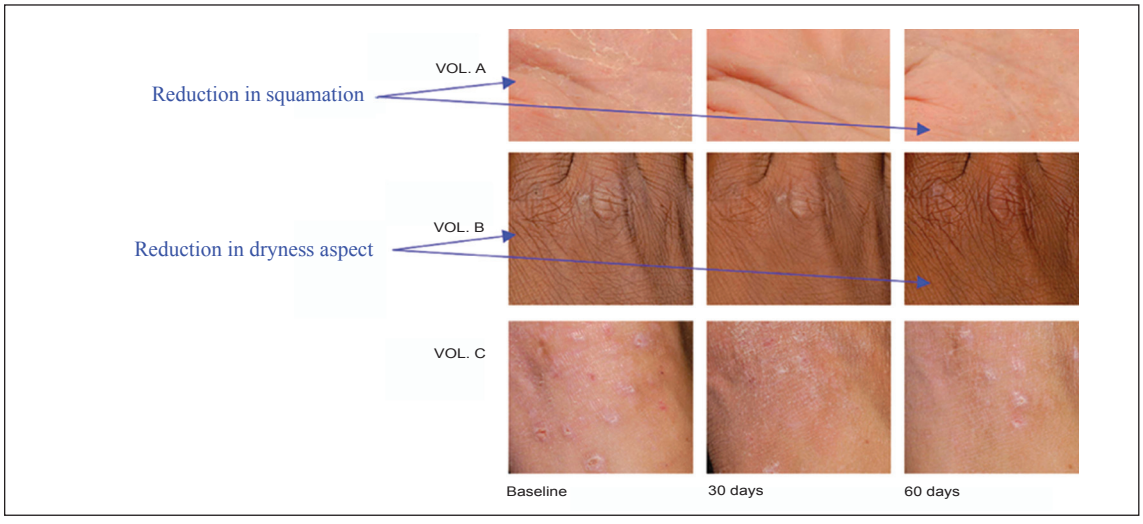

Figure 7 – Squamation, dryness, and general aspects of skin at baseline, during, and after treatment.

Regarding tolerability, 8 volunteers have complained; 2 had skin irritation; 3 had worsening of pruritus; 1 had a higher number of lesions of atopic dermatitis, 1 presented pruritic and papular lesions; 1 reported worsening of the eczema, 1 presented allergy in upper limbs; and 1 reported a burning sensation. The body regions reported in the complaints were: face (2 volunteers), upper limbs (3 volunteers), lower limbs (1 volunteer), and neck (3 volunteers). The time of product use in which complaints emerged was diverse, but it prevailed after the immediate application (five volunteers), up to 10 days of use (1 volunteer), up to 20 days of use (1 volunteer), up to 30 days of use (1 volunteer).

DISCUSSION

Atopic dermatitis is a chronic inflammatory disease with varied clinical manifestations. The disease major stigmas are pruritus, xerosis, eczema and lichenification, generally of symmetrical distribution.[6] Treating these symptoms go beyond drug therapy, it involves a series of measures that imply a change in lifestyle of patients, such as short showers, using mild and emollient soaps, which are often considered low priority when in fact they should be the fundamental of therapy in atopic individuals.[16]

Pruritus is defined as an unpleasant sensation that evokes the desire or reflex to scratch, and, besides being a symptom, it is responsible for the onset of new symptoms and permanence of AD lesions. The multiple mechanisms of onset and permanence of pruritus are poorly understood. Recent studies on pathophysiology of chronic pruritus, especially pruritus in atopic dermatitis, have shown changes in the number of nerve fibers of damaged skin.[9] It is believed that there is an increase in the number of type C unmyelinated sensory fibers, which are responsible for conducting pruritic stimulus by direct stimulation of histamine, peptides, and neuropeptides released after skin injury. External factors would act as a trigger activating neuropeptides that stimulate sensory fibers, directly or indirectly, through the release of mediators from

mast cells and keratinocytes.[9] With regard to neuropeptides, the most important are substance P and the peptide related to calcineurin. The first is released by the action of mast cell tryptase on the proteinase-activated receptor-2 (PAR-2) of nerve fibers in skin; the second causes vasodilatation and increases vascular permeability.[13] At the end, the primary afferent pathway activation results in spread of anterograde stimulus to central nervous system, particularly the thalamus, and retrograde stimulus to axon terminal fibers, which added to the changes in neuropeptides induce local inflammation, worsening as the mechanism of injury remains.[9,13]

Based on pathophysiology in the genesis of pruritus, we concluded that it requires treatment with different drugs according to the mechanism of origin, degree, and chronicity of its existence.[10,14] Antihistamines will act by inhibiting the release of histamine granules by mast cells, blocking the activation of sensory nerve fibers, which is vital in pruritus treatment of AD and is one of its major causes.[10,14]

However, if there is no blockage of external factor triggers through the restructuring of atopic skin, the release of neuropeptides and activation of PAR-2 will be maintained, establishing a route of pruritus transmission that will not respond to antihistamines.[14]

Xerosis is defined as the result of an epidermal disorder that reduces the capacity of the stratum corneum to retain water by increasing its transepidermal loss. The amount of water normally ranges between 15-20%.[16] When this percentage drops below 10, changes in the stratum corneum function occur and the skin becomes scaly and dry. In atopic patient there is still a decrease of ceramides with increased space between corneocytes.[16] Deterioration of ceramide synthesis in stratum corneum tends to perpetuate the maintainer cycle of xerosis by destroying the intercellular lipid film, leading to dysfunction of keratinocytes differentiation, amplifying the inflammatory response, and allowing the entry of external antigens.[16]

Emollients act by reconstituting the components responsible for elasticity and epidermal barrier function. Moisturizers are substances that attract and retain water in a passive way, while humectants have active hygroscopic function. Glycerol is a humectant with a key role in maintaining stratum corneum hydration, since changes in aquaporin-3, a carrier of water/glycerol, leads to decrease in hydration and loss of elasticity that can only be corrected by glycerol topical application.[16] Another important function of this substance is to have direct antipruriginous action.[16] Colloidal oatmeal has a complex composition, being rich in water, proteins, carbohydrates, lipids, minerals, and vitamins. It acts in several important points, such as restructuring cellular and intercellular components by the richness of oligoelements; is highly moisturizing; has anti-inflammatory, soothing, and antipruritic action. Biochemically, it is an interesting component to emollients, since it increases the compatibility between element components.[16]

Improvement in hydration, eczema and, consequently, in pruritus presented by patients in the study demonstrates that the replacement of intercellular stratum corneum constitutional elements prevents water loss, restore the local protection function, and blocks external and microenvironmental stimuli that trigger pruritus.

The acid mantle of the stratum corneum is of paramount importance in the permeability of the skin as well as for antibiotic regulation.[17] Skin pH is directly affected by exogenous agents, such as detergents, topical products, and cosmetics.[17] Therefore, the use of products in pH 5.5 range (physiological pH) is important for prevention and treatment of skin diseases in which change in pH is one of the elements in pathogenesis, such as atopic dermatitis, contact dermatitis, and ichthyosis.[17] The different pH of formulations used by the two groups did not influence the results, probably because both are close to the skin physiological pH (4.5-6.5) and among each other.

Regarding product tolerability of subjects studied, 8 reported some kind of discomfort after moisturizer application. Of these, 7 reported discomfort at the beginning of treatment (first week of use), but the sensation was characterized as mild and did not require the emollient suspension, showing skin improvement with continued use of product.

This discomfort feeling probably occurred because the skin had a high degree of damage. For this reason, the replacement of water and the main elements to the formation of intercellular barrier as already described have improved the skin structure with continued use, causing discomfort to cease completely. The other volunteer had discomfort in the second fortnight of cream use, but it was mild and disappeared with continued use. Probably the reason for discomfort was the same as described above for the other volunteers. Therefore, we can conclude that discomfort was due to changes in skin caused by disease, but they were mild and did not cause use discontinuation, as is customary among patients with atopic dermatitis, and these patients did show improvement with product.

CONCLUSIONS

The two formulations studied did not show significant differences in performance, probably because both pH values used were similar and close to skin physiological pH.

The use of formulas with pH close to that in normal skin provided a significant improvement in pruritus in 59% of the assessments made by volunteers and in 52% made by clinical evaluators. Volunteers rated 52% of improvement in xerosis and clinical evaluators rated 43%.

After 30 days of treatment with the studied lotions, the level of moisture in region with eczema equaled the level of hydration in region without eczema (control region). After 60 days of treatment, there was an improvement of 79% in level of skin hydration in regions with eczema, as measured by corneometry.

Signs of discomfort such as skin irritation, increased itching, worsening of eczema, and burning sensation were mild and resolved spontaneously with the product continued use. Therefore, lotions at pH close to that of normal skin have low rates of adverse effects, are safe for use in atopic patients, in addition to provide hydration improvement, pruritus and eczema reduction.

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