

Lack of Efficacy of Topical Furfuryl Palmitate in Pediatric Atopic Dermatitis: A Randomized Double-Blind Study

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■ Abstract

Introduction: Atopic dermatitis is a common disease in children. It is usually treated with topical steroids and/or calcineurin inhibitors in association with emollients but topical antioxidants have been recently introduced as a therapeutic option for children. The aim of this study was to evaluate the efficacy and tolerability of furfuryl palmitate, a new antioxidant molecule, in a multicenter, randomized, double-blind, vehicle-controlled study.

Patients and Methods: Children with atopic dermatitis were randomized into 2 groups treated for 2 weeks. One group of children (n=60) was treated with a basic emollient cream and the other (n=57) was treated with the same cream enriched with furfuryl palmitate.

Results: In both groups, there was a significant reduction ($P<.001$) in atopic dermatitis—measured using the SCORAD index—after 14 days. The reduction in the per-protocol analysis was higher for the basic cream. Treatment success was defined as a reduction of 20% or more in the SCORAD index from baseline to day 14. Patients who used treatment not permitted by the protocol were also considered treatment failures. The intention-to-treat analysis showed 70% positive results for the basic treatment and 29% for the treatment containing furfuryl palmitate ($P<.0001$) with a number needed to treat of 2.4 (95% confidence interval, 1.6-4.6). The emollient cream without furfuryl palmitate was observed to be more efficacious by pediatricians and parents, and no differences were reported between the 2 products in terms of tolerability.

Conclusions: Both products proved to be efficacious in treating atopic dermatitis in children, but the emollient cream not containing furfuryl palmitate showed better clinical efficacy.

Key words: Atopic dermatitis. Children. Furfuryl palmitate. Topical administration.

■ Resumen

Introducción: La dermatitis atópica es una enfermedad común en los niños. Se trata normalmente con esteroides tópicos y/o inhibidores de la calcineurina en asociación con emolientes pero los antioxidantes tópicos se han introducido recientemente como una opción terapéutica para niños. El objetivo del estudio fue evaluar la eficacia y tolerabilidad del furfural palmitato, una nueva molécula antioxidante, en un estudio multicéntrico, aleatorizado, doble ciego, controlado con vehículo.

Pacientes y Métodos: Se aleatorizaron niños con dermatitis atópica en 2 grupos tratados durante 2 semanas. Un grupo de niños (n=60) fue tratado con una crema básica emoliente y el otro (n=57) fue tratado con la misma crema enriquecida en furfural palmitato.

Resultados: En ambos grupos, hubo una reducción significativa ($P<.001$) en la dermatitis atópica usando el índice SCORAD tras 14 días. La reducción en el análisis por protocolo fue mayor con la crema básica. El éxito del tratamiento se definió como una reducción de un 20% o más en el índice SCORAD desde el momento basal hasta el día 14. Los pacientes que emplearon tratamientos no permitidos por el

protocolo fueron también considerados fracasos de tratamiento. El análisis por intención de tratar mostró un 70% de resultados positivos para el tratamiento básico y 29% para el tratamiento que contenía furfuryl palmitato ($P < 0,0001$) con un número necesario a tratar de 2,4 (Intervalo de confianza al 95%, 1,6-4,6). Los pediatras y padres observaron que la crema emoliente sin furfuryl palmitato era más eficaz, y no se notificaron diferencias entre los 2 productos en términos de tolerabilidad.

Conclusiones: Ambos productos probaron ser eficaces en el tratamiento de la dermatitis atópica en niños, pero la crema emoliente sin furfuryl palmitato mostró mayor eficacia clínica.

Palabras clave: Dermatitis atópica. Niños. Furfuryl palmitato. Administración tópica.

Introduction

Atopic dermatitis is one of most common allergic pathologies in children and is usually treated with topical corticosteroids and/or calcineurin inhibitors, often in association with emollients [1-3]. Alternative topical drugs, however, are often preferred because of parental concern about the adverse effects associated with corticosteroids [4,5].

The mechanisms underlying skin inflammation in atopic dermatitis are not completely understood, although some studies have suggested the involvement of oxidative stress and altered antioxidant defenses in the pathophysiology of acute exacerbation of atopic dermatitis in children [6-8].

The aim of this study was to evaluate the efficacy and tolerability of furfuryl palmitate, an antioxidant molecule used in topical treatment that was recently patented in Italy and that has proven to be useful in the management of several types of dermatitis in an open study [9]. We performed a double-blind study in which we compared an emollient cream with the same cream enriched with furfuryl palmitate in children with atopic dermatitis.

Methods

We randomized 117 children aged between 3 months and 14 years into 2 treatment groups. All the children were outpatients from different pediatric allergology centers in Rome and they all had a diagnosis of atopic dermatitis based on the UK Working Party's diagnostic criteria [10]. Patients were required to abstain from all kinds of topical and systemic treatment for at least 1 week before the start of treatment and to make no changes to their usual lifestyle (diet, allergen avoidance, etc) (Table).

Randomization was performed using a computer-generated list. Three visits were scheduled for each child at 7 days apart (D_0 , D_7 , and D_{14}) (Figure 1) and atopic dermatitis severity was evaluated using the SCORAD index [11] (ScoradCard software; TPS Production, Rome, Italy) (Figure 2). This index is a validated tool that has proven useful for minimizing interobserver and intraobserver variability [12]. In the SCORAD index, mild eczema is defined as a score of under 25, moderate eczema as a score of 25 to 50, and severe eczema as a score of over 50 [11].

Table. Demographic and Clinical Characteristics of Study Group

	Group A ^a	Group B ^b	A vs B P value
Patients, No	60	57	
Male, %	60.0	61.4	>.05
Mean (SD) age, mo	51.7 (38.8)	52.7 (43.8)	>.05
Family history of atopy, ^c %	85.0	82.5	>.05
Mean (SD) age of onset of AD, mo	4.2 (3.1)	4.0 (3.5)	>.05
Mean (SD) duration of AD, mo	48.1 (42.0)	44.5 (43.0)	>.05
Mean (SD) SCORAD index ^d	25.6 (10.1)	28.1 (10.6)	>.05
Diagnosis of asthma, %	18.3	17.5	>.05
Diagnosis of allergic rhinitis, %	18.6	19.3	>.05
Diagnosis of food allergy, %	28.8	39.3	>.05

Abbreviations: AD, atopic dermatitis; SPT, skin prick test.

^a Treatment with basic emollient cream

^b Treatment with emollient cream containing furfuryl palmitate

^c At least 1 first-degree relative with atopy.

^d Measure of atopic dermatitis severity, evaluated using ScoradCard v 2.0 software (TPS Production, Rome, Italy).

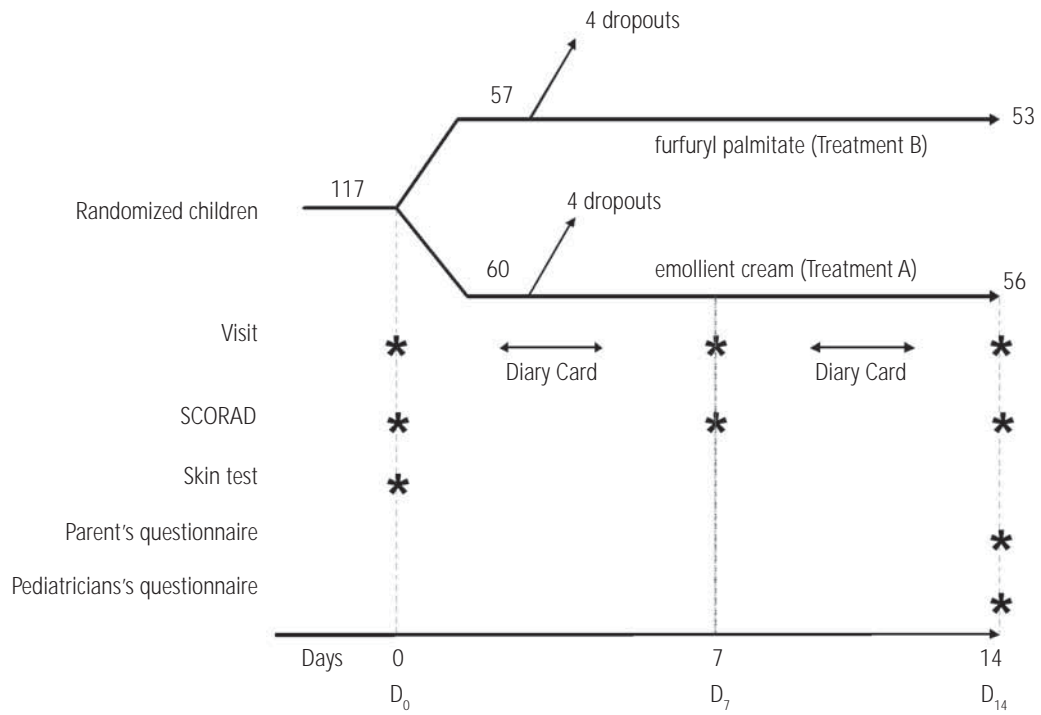


Figure 1. Study design.

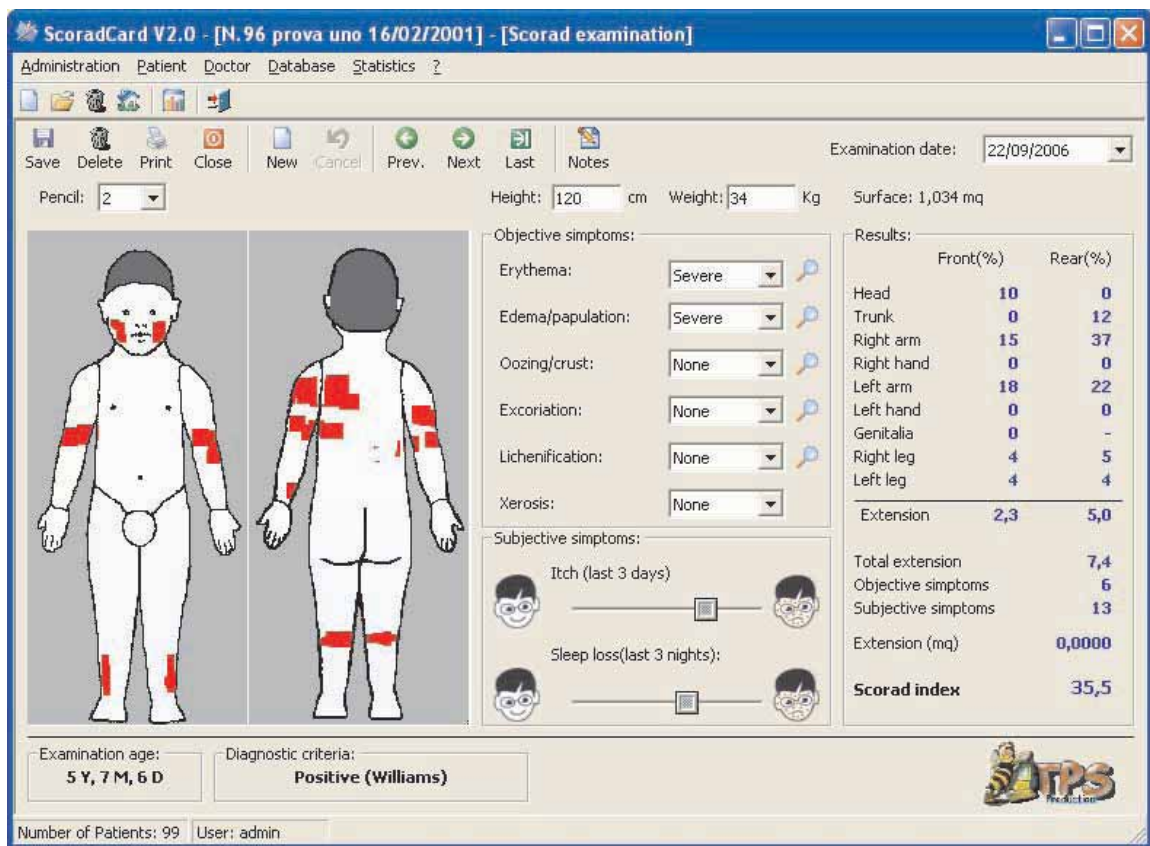


Figure 2. SCORAD index (measure of atopic dermatitis severity) evaluated using ScoradCard v 2.0 software (TPS Production, Rome, Italy).

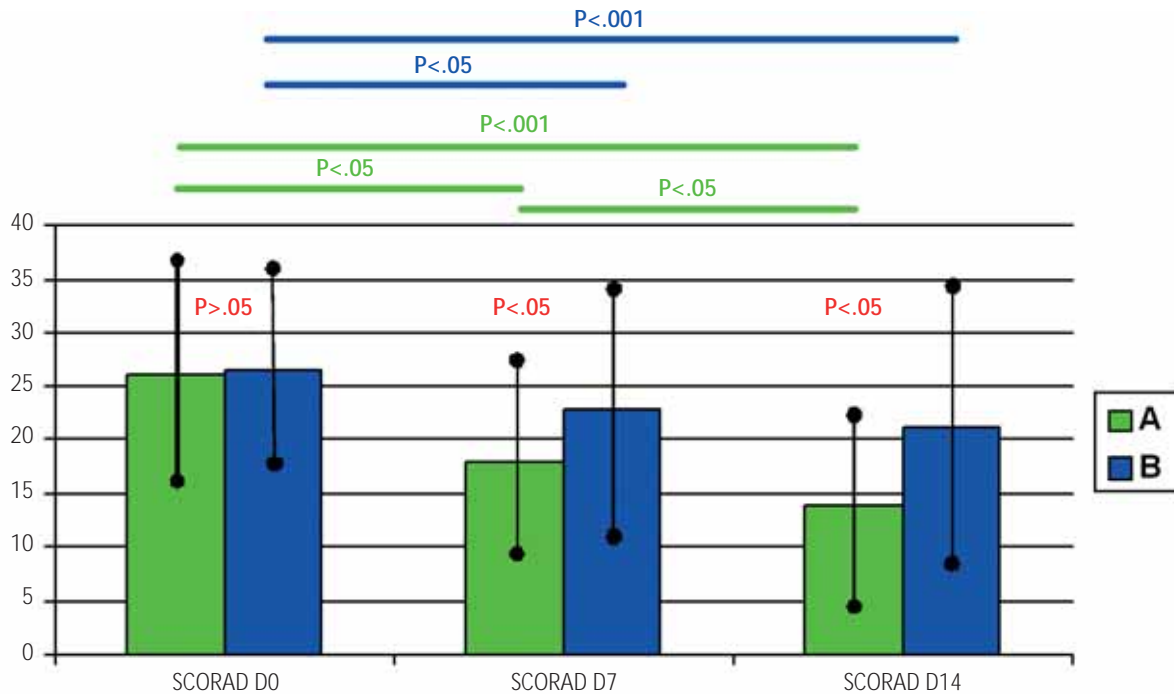


Figure 3. Mean (SD) SCORAD index (measure of atopic dermatitis severity) (ScoradCard v 2.0 software; TPS Production, Rome, Italy) for group A (basic product, n=49) and group B (basic product and furfuryl palmitate, n=39) at baseline and at days 7 and 14 (per-protocol analysis).

Examining pediatricians and parents evaluated the efficacy and tolerability of the products using a purpose-designed questionnaire at D₁₄. Efficacy was rated as worsening, inexistent, poor, good, or very good, and tolerability was rated as poor, good, or very good.

The study was double blind, with the key code disclosed only after statistical evaluations. The 2 topical products had an identical color, smell, and consistency and were indistinguishable to both parents and examining pediatricians. Product A was an emollient cream containing various antioxidant molecules (superoxide dismutase, 18-β-glycyrrhetic acid, vitamin E, and α-bisabolol) and product B was the same emollient cream enriched with furfuryl palmitate. Both products were provided by the same manufacturer (ICIM International Srl, Milan, Italy). The products were applied, to eczematous areas only, twice a day for 2 weeks. The finger tip unit (FTU) was used to standardize treatment, with 1 FTU being used to treat an area of skin twice the size of the flat of an adult's hand with the fingers together [13]. Treatment with systemic or topical corticosteroids, topical immunomodulators, and topical or oral antihistamines was not allowed. When used, however, the details of these treatments were recorded in a diary and the corresponding patients were considered treatment failures in the intention-to-treat analysis. These patients were asked to continue with their usual lifestyle and dietary habits (no changes) for what remained of the study. Atopic status was assessed at the D₀ visit using skin prick tests if the skin condition allowed such a procedure. The tests were performed with a standard panel of commercial extracts—including

Dermatophagoides pteronyssinus, grass pollen, *Parietaria judaica*, olive, cat dander, *Alternaria*, hen's egg, wheat, and codfish (Stallergènes SA, Antony, France)—and a positive (histamine 1%) and negative (isotonic saline) control. For cow's milk, the prick by prick method [14] with pasteurized milk was used. The study was approved by the ethics committee at each participating center.

Statistical Analysis

Sample size was calculated on the basis of an expected improvement in atopic dermatitis severity of at least 20% from baseline (D₀) to the last visit (D₁₄) (2-sided test with an α error of 0.05 and a β error of 0.8). Per-protocol and intention-to-treat analyses were performed. Frequency comparisons between the 2 groups were examined using the χ² test or the Fisher exact test where appropriate. The *t* test was used for mean comparisons. Correlation of categorical data was analyzed using the Spearman correlation coefficient. Statistical significance was set at a value of *P* < .05. The SPSS software package version 11.0 (SPSS Inc., Chicago, Illinois, USA) was used for all computations.

Results

Of the 117 children enrolled, 109 completed the study and 8 (4 from each group) participated in the first visit only (dropout rate, 7%). The mean (SD) SCORAD index for these dropouts was 22.72 (8.86) (95% confidence interval [CI],

15.3-30.1) ($P > .05$ compared to patients that completed the study). Fifty-six children used product A and 53, product B (containing furfuryl palmitate). Seven (12.5%) of the children in group A took drugs not permitted by the protocol compared to 14 (26.4%) in group B. The difference, however, was not statistically significant and the mean SCORAD index at baseline for these 21 children was 30.8 (95% CI, 25.7-35.9) ($P > .05$ compared to per-protocol patients).

Our per-protocol analysis included 49 children from group A and 39 from group B. Figure 3 shows the variations in the SCORAD index at days 7 and 14.

The mean baseline SCORAD index was 26 for group A and 26.6 for group B ($P > .05$). The reduction in atopic dermatitis severity was significant for both groups between D_0 and D_7 ($P < .05$) and between D_0 and D_{14} ($P < .001$). It was also statistically significant between D_7 and D_{14} but only for group A ($P < .05$). The mean SCORAD index differed between groups at D_7 and D_{14} ($P < .05$). Treatment success was defined as a reduction of 20% or more in the SCORAD index from baseline to D_{14} without the use of treatment not permitted by the protocol. The intention-to-treat analysis of 102 patients (dropout rate, 12.8%) evaluated at D_0 and D_{14} showed 38 positive results for the 54 children treated with product A (70%) and 14 for the 48 patients treated with product B (29%) ($P < .0001$). The calculated number needed to treat was 2.4 (95% CI, 1.6-4.6). Taking into account the overall treatment failures (dropouts at D_0 and D_{14} and protocol violators), the statistical significance did not even change in the sensitivity analysis scenario ($P = .025$, data not shown).

Both pediatricians and parents rated the emollient cream without furfuryl palmitate to be more efficacious than the cream with furfuryl palmitate ($P = .016$) with a Spearman's correlation coefficient of $r = 0.9$ ($P < .01$). No differences were reported regarding the tolerability of the 2 products (data not shown).

Discussion

The use of emollients is considered standard therapy for atopic dermatitis [1-3,15], although only a few studies have evaluated the effects of emollients alone in this treatment [4,5,16].

The use of topical or oral antioxidants was recently suggested as a possible option for treating skin degenerative processes due to oxidative stress [6-8]. The emollient cream utilized in the present study contains various antioxidant molecules, described in the Methods section. It has been claimed that the combined action of these active agents may protect skin from cell damage that activates the inflammatory syndrome, and that furfuryl palmitate has a strong quenching ability towards the singlet oxygen, considered one of the main factors responsible for skin aging and many topical pathologies [9]. Although the corresponding study showed the efficacy of furfuryl palmitate, it was an open trial in which different types of dermatitis were treated. The authors reported a significant decrease in symptoms in children aged between 3 months and 12 years but they used an arbitrary rather than a validated score index.

We defined treatment success as an improvement of 20% or more in the SCORAD index at D_{14} (2 weeks) compared to D_0 (baseline). Even though it could be argued that this improvement is within the range for a placebo effect, it is an acceptable result for an emollient cream considering the risk/benefit ratio. This would not be the case for a topical corticosteroid, for which we would expect a better result.

Our study showed that while the emollient cream containing furfuryl palmitate was efficacious to a certain extent, the results were less clinically relevant than those observed for the same cream not containing the active ingredient. Indeed, the SCORAD improvement after 14 days, albeit statistically significant, was only 5 points for product B (containing furfuryl palmitate) compared to 12 points for product A. Moreover, over twice as many patients in group B as in group A needed rescue medication (26% vs 12%, respectively).

One hypothesis that might explain our findings is that the cream-based vehicle is already rich in antioxidants, albeit nonstandard antioxidants such as superoxide dismutase. Assuming that these antioxidants yielded benefits, it is possible that the cream base was already eliciting the maximal possible effect, meaning that any additions would not have increased the benefit. Another hypothesis is that the cream containing furfuryl palmitate acted as an irritant, although no statistical differences were found for the tolerability of the 2 products reported by pediatricians and parents. It should be pointed out, however, that the enriched cream was reported to be less well tolerated, with complaints of itching and burning sensation after application (data not shown).

We chose to use the UK Working Party's criteria to diagnose atopic dermatitis [10] because they are simple and quick to apply and also have good sensitivity and specificity, not only for epidemiologic studies but also for clinical trials, as has been recently shown [17].

Adherence to therapy, though not specifically measured, was good thanks to the short duration of the study. Such a short observation period (14 days) is, however, one of the study's limitations because atopic dermatitis is a highly fluctuating disease and the results may, therefore, be due to chance. Another limitation is the absence of a control group treated with a true placebo (vehicle only) and another group treated with no emollient product.

Our findings, and particularly those related to the emollient cream without furfuryl palmitate, support previous findings [5] that the regular use of adjunctive drugs can reduce the use of topical corticosteroids.

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