Original Contribution

Specific gel-cream as adjuvant to oral isotretinoin improved hydration and prevented TEWL increase – a double-blind, randomized, placebo-controlled study

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Summary

Background Hydrating and emollient products are often recommended to patients under isotretinoin therapy to control the most frequent mucocutaneous side effects and to improve adherence to treatment.

Aims To assess, using noninvasive biophysical tests, the clinical and instrumental effectiveness of a hydrating *gel-cream* compared with placebo as an adjuvant to isotretinoin for treatment of facial skin in patients with inflammatory acne.

Methods Prospective, double-blind, randomized study, using MULTI SKIN MC750, on the adjuvant effect of a hydrating gel-cream for acne (active product) *vs.* a gel-cream without active substances (placebo). Follow-up lasted 3 months.

Results Sixty-six patients were included. Thirty-four were administered the active product, and 32 placebo. Though the number of lesions fell significantly in both groups, the mean number of papules on day 30 was significantly lower in the active product group. The active product group showed a significant increase in hydration, while the placebo group showed a significant increase in transepidermal water loss (TEWL). Seborrhoea decreased significantly in both groups; there were no differences between them.

Conclusions Compared with placebo, the specific gel-cream with active products as an adjuvant to oral isotretinoin improved hydration, prevented TEWL increase, and reduced inflammatory acne lesions after 30 days.

Keywords: acne, treatment, oral isotretinoin, adjuvant treatment, emollients, gel-cream

Introduction

Oral isotretinoin remains the most effective of the treatments currently available for acne.[1–4] Its effectiveness is dependent on the accumulated dose and any treatment must be continued long enough to reach the standard accumulated doses of 120–150 mg/kg.

The drug's potential side effects, principally in the skin and mucosa, make adherence to treatment difficult and lead many physicians to reduce the doses.[1,2,5] Therefore, the control of these side effects and their impact on patient compliance is the key to treatment success. Hydrating products, which improve the hydration and softness of the skin, are especially indicated for relieving xerosis in

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patients undergoing therapy with oral isotretinoin. However, not all these products are well suited for treating acne: many of them are comedonegenic and potentially irritating, and may actually aggravate the disease.[6]

One of the hydrating products currently available for the treatment of acne is a specific gel-cream (Acniben Rx®; Laboratorios Isdin, S.A., Barcelona, Spain) which contains hyaluronic acid, biosaccharide gum-2 and glycerine. Previous studies of this product as adjuvant treatment in pharmacological approaches to acne show that it reduces xerosis, erythema, and pruritus in patients undergoing treatment with isotretinoin.[7,8] The aim of this study was to evaluate the effectiveness of this gel-cream on mucocutaneous symptoms following treatment with oral isotretinoin *vs.* a placebo in a randomized, controlled study using noninvasive biophysical tests.

Materials and methods

This was a prospective, double-blind, randomized study using clinical and instrumental tests to compare the effectiveness of a specific hydrating gel-cream containing hyaluronic acid, biosaccharide gum-2 and 7% glycerine (active group) *vs.* placebo (gel-cream only with excipients and 3% glycerine) as adjuvant treatment in patients with inflammatory acne treated with oral isotretinoin.

Patients were recruited from the private practices of the dermatologists having diagnoses of long-term mild, moderate, or severe acne refractory to other treatments and requiring treatment with oral isotretinoin. Before inclusion, all patients (or their parent or legal guardian) signed an informed consent form.

Experimental design

The study lasted 3 months. Three control visits were scheduled, at the start of the treatment (d0), at 30 days (d30), and at 90 days (d90). Each patient was prescribed anti-acne treatment in the form of isotretinoin capsules, in daily doses of between 0.4 and 0.7 mg/kg during the first month. The dose was later regulated in accordance with the systemic adverse effects. All participants were given a cleansing gel which they were instructed to use twice a day, in the morning and at night, throughout the study. The use of any other additional cosmetic products on the face was prohibited.

Clinical evaluations comprised assessment of the severity, facial lesion count, the incidence of adverse effects (xerosis, cheilitis, and dermatitis), and the intensity of the cutaneous signs/symptoms following treatment with isotretinoin (dryness, desquamation, pruritus, and erythema) using visual analog scales from 0 to 10.

The instrumental evaluations were performed on the skin of the cheek, after 24 h without using creams or make-up. The MULTI SKIN test centre MC750 (Courage + Khazaka, Cologne, Germany) was used to measure the amount of sebum, hydration, and transepidermal water loss (TEWL).

Statistical analysis

The statistical analysis was performed using the SPSS 13.0 for Windows statistical package. As statistical tests we used one-factor variance analysis (ANOVA) or Mann–Whitney *U*-test in the comparisons between groups, and Student's *t*-tests for paired data or Wilcoxon tests for the comparisons over time (evolution), separately in each group. For the dichotomous variables, chi-squared tests were used. The level of significance was set at $P < 0.05$ for all tests.

Results

Sixty-six patients were included, 34 in the active group and 32 in the placebo group, ranging in age from 15 to 43 years (Table 1).

The degree of acne fell significantly in both groups ($P < 0.001$) after 1 month (d30) and after 3 months (d90) of treatment. In the active group, the mean number of comedones, pustules, and papules fell significantly at

Table 1 Characteristics of the sample

	Placebo group (n = 32)	Gel-cream group (n = 34)	*P*-value
Sex (%)			
Male	20/32 (62.5)	16/31 (51.6)*	0.450
Female	12/32 (37.5)	15/31 (48.4)*	
Age			
Mean [95% CI]	20.19 [18.1–22.3]	22.06 [19.9–24.3]	0.268
Maximum-minimum	43–15	38–15	
Grade of acne (%)			
Mild	2/32 (6.3)	6/34 (17.6)	0.211
Moderate	17/32 (53.1)	12/34 (35.3)	
Severe	13/32 (40.6)	16/34 (47.1)	
Isotretinoin dose (mg/kg)			
Mean [95% CI]	0.49 [0.47–0.51]	0.52 [0.49–0.55]	0.125
Average number of lesions			
Comedos	41.88	53.88	0.339
Pustules	21.34	14.18	**0.033****
Papules	21.34	16.18	0.092
Nodules or pseudocyst	1.97	2.21	0.749

*Sex missing n = 3 cases in gel-cream group.
**statistically significant.

d30 and d90 ($P < 0.001$), and the number of pseudocysts/nodules at d90 ($P < 0.01$). In the placebo group, a significant reduction was also found in the number of comedones, pustules, and papules, but this group did not present a significant improvement in the number of pseudocysts or nodules (Table 2). The comparison between groups did not show significant differences in terms of the number of comedones and pustules. Nonetheless, the mean number of papules at d30 was significantly lower in the hydrating gel-cream group (Fig. 1).

The proportion of patients presenting xerosis after 3 months of therapy was significantly lower in the active group (40.6% *vs.* 64.5%; $P < 0.05$). There were no significant differences in terms of the incidence of cheilitis (93.8% *vs.* 100%) or dermatitis (31.3% *vs.* 32.3%). The clinical evaluation of the mucocutaneous symptoms did not show significant differences between groups, although the active group tended to score lower than the placebo group for dryness (4.13 *vs.* 4.42), desquamation (3.34 *vs.* 3.63), pruritus (0.61 *vs.* 1.35), and erythema (2.56 *vs.* 3.23).

The seborrhea fell significantly in both groups; there were no differences between them. Hydrometry only showed a significant increase in hydration in the active group at d30 (41.88 *vs.* 47.44; $P < 0.01$), while in the placebo group no significant changes were detected in any of the controls (Fig. 2). As for TEWL, the placebo group showed a significant increase [from 9.09 (d0) to 10.69 (d30) and to 10.31 (d90); both $P < 0.05$], while no significant changes were detected in the active group (Fig. 3).

The physician's evaluation of the effectiveness, tolerance, and satisfaction with the products did not show significant differences between groups and was good or excellent for most cases. As for the patients, most of their final ratings were good or excellent in both groups. However, the final rating of the effect was higher in the active group (Table 3).

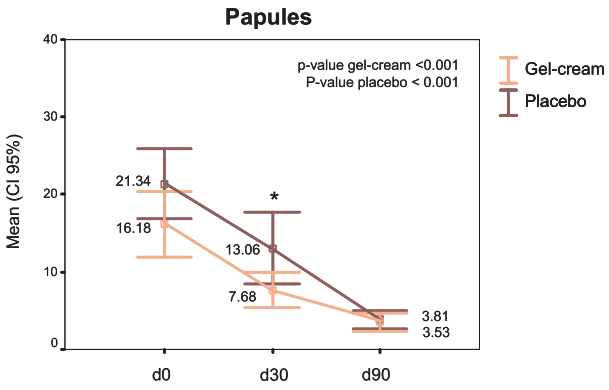

Figure 1 Reduction in the number of papules in both groups.

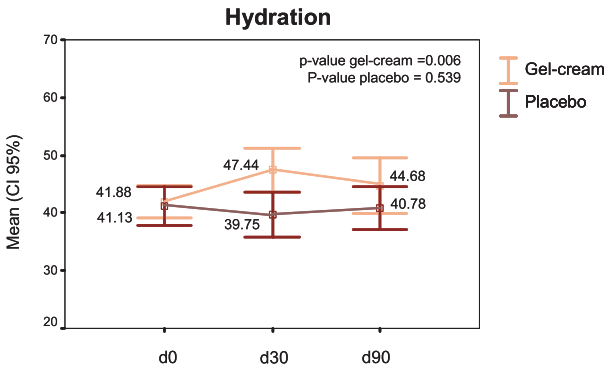

Figure 2 Evolution of hydration in both groups.

Table 2 Clinical evolution of the lesions

	Placebo group (n = 32)	P-value*	Gel-cream group (n = 34)	P-value*
Comedones (mean)				
Day 30	25.91	<0.001	35.71	<0.001
Day 90	10.50	<0.001	14.29	<0.001
Pustules (mean)				
Day 30	9.81	<0.001	8.56	<0.001
Day 90	3.06	<0.001	3.00	<0.001
Papules (mean)				
Day 30	13.06	0.003	7.68	<0.001
Day 90	90 3.81	<0.001	3.53	<0.001
Nodules or pseudocyst				
Day 30	1.47	0.504	1.56	0.181
Day 90	1.09	0.253	1.09	0.008

*P-value comparison with the number of initial lesions.

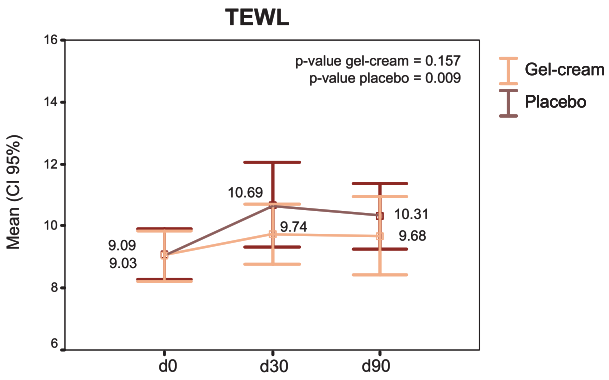

Figure 3 Evolution of transepidermal water loss (TEWL) in both groups.

Table 3 Subjective rating (0 = poor, 1 = moderate, 2 = good, 3 = excellent) of products by physicians and patients

	Placebo group (n = 31)	Gel-cream group (n = 32)	P-value*
Subjective rating by physicians			
Satisfaction (mean)	3.06	3.28	0.226
Efficacy (mean)	3.06	3.38	0.083
Tolerability (mean)	3.39	3.34	0.958
Subjective rating by patients			
Efficacy (mean)	3.00	3.22	0.201
Tolerability (mean)	3.32	3.41	0.624
Speed of action (mean)	3.0	3.41	0.054
Pleasantness (mean)	3.13	3.38	0.167
Satisfaction (mean)	3.06	3.34	0.242

*P-value comparison between the groups.

Discussion

Oral isotretinoin is the treatment of choice for severe inflammatory acne and is considered an alternative treatment for patients with moderate and long-term mild inflammatory acne with poor response to other treatments.[9–11] The use of hydrating and emollient products is often recommended to control the most frequent mucocutaneous side effects[1,2,12] and previous studies suggest that specific gel-cream (Acniben Rx®) possesses hydrating and anti-inflammatory properties and is potentially beneficial.[7,8]

The results showed a significant reduction in the inflammatory and noninflammatory lesions in both groups from the first month of treatment onward. Nonetheless, two differences were observed between the groups: after the first month of treatment, the mean number of papules in the gel-cream group was significantly lower than in the placebo group, suggesting that the gel-cream accelerates the resolution of the inflammatory lesions, and only the gel-cream group showed a significant reduction in the mean number of nodules after 90 days and maybe was not long enough for a significant fall in the nodules in the placebo group.[9] Both the speed in the reduction of the nodules and the number of papules are probably due to the anti-inflammatory effect of the biosaccharide gum-2 which blocks the inflammatory substances interleukin and tumor necrosis factor-α.[13]

The study also showed that the use of the hydrating gel-cream significantly reduced the incidence of xerosis compared with placebo. This difference can be attributed to the active agents in the cream gel: the higher concentration of glycerine necessary to maintain the normal hydration,[14] hyaluronic acid, a hygroscopic substance which is a constituent of stratum corneum[15] and helps to keep the skin hydrated,[16] and the biosaccharide gum-2, a polysaccharide rich in rhamnose which also produces a hydrating effect.

Although there were no significant differences, the hydrating gel-cream with active ingredients showed a clear tendency to reduce the intensity of irritating signs following treatment with isotretinoin. This trend may be attributed to the improved hydration and the protective effect on barrier function.[17]

The level of sebum was lowered by treatment with oral isotretinoin and was not altered by the use of the cream gel, demonstrating that the active ingredients are substances that do not induce sebum production. Hydration increased significantly after the first month in the gel-cream group and indeed remained high during the rest of the study. In contrast, the placebo group showed no differences in hydration throughout the study. This may be due to the fact that the placebo contains a lower proportion of glycerine.[14]

No differences were found in the behavior of the TEWL in the two groups. Nonetheless, we observed a significant increase in the mean TEWL in the placebo group. The preservation over time of the barrier function in the gel-cream group was attributed to hyaluronic acid which helps to maintain the integrity of the barrier by influencing cell–cell and cell–matrix contacts and possibly by regulating keratinocyte differentiation,[16] and to the biosaccharide gum-2 which acts as a protector of hyaluronic acid reducing its breakdown.[18]

Physicians and patients rated the products highly and both products were well tolerated, hence the active ingredients (hyaluronic acid, biosaccharide gum-2 and glycerine) did not increase the incidence of side effects.

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