

ORIGINAL ARTICLE

The effect of a corticosteroid cream and a barrier-strengthening moisturizer in hand eczema. A double-blind, randomized, prospective, parallel group clinical trial

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Abstract

Background Hand eczema is a common and persistent disease with a relapsing course. Clinical data suggest that once daily treatment with corticosteroids is just as effective as twice daily treatment.

Objectives The aim of this study was to compare once and twice daily applications of a strong corticosteroid cream in addition to maintenance therapy with a moisturizer in patients with a recent relapse of hand eczema.

Methods The study was a parallel, double-blind, randomized, clinical trial on 44 patients. Twice daily application of a strong corticosteroid cream (betamethasone valerate 0.1%) was compared with once daily application, where a urea-containing moisturizer was substituted for the corticosteroid cream in the morning. The investigator scored the presence of eczema and the patients judged the health-related quality of life (HRQoL) using the Dermatology Life Quality Index (DLQI), which measures how much the patient's skin problem has affected his/her life over the past week. The patients also judged the severity of their eczema daily on a visual analogue scale.

Results Both groups improved in terms of eczema and DLQI. However, the clinical scoring demonstrated that once daily application of corticosteroid was superior to twice daily application in diminishing eczema, especially in the group of patients with lower eczema scores at inclusion.

Conclusions Twice daily use of corticosteroids was not superior to once daily use in treating eczema. On the contrary, the clinical assessment showed a larger benefit from once daily treatment compared with twice daily, especially in the group of patients with a moderate eczema at inclusion.

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Conflict of interest

KTS, NM, HH, GM, CLH, JF and BM are paid consultants to ACO Hud Nordic AB. ML and KW are employed by ACO Hud Nordic. This study was funded by ACO Hud Nordic AB and Knowledge Foundation, Sweden.

Introduction

Hand eczema is a common and persistent disease with a relapsing course and variable disease duration.¹ Treatments include topical corticosteroids, phototherapy and chemotherapy.² Tradition suggests that patients should apply the drugs several times daily under the theory that the rate of clearance of the eczema should be related to the application frequency. However, clinical data suggest that once daily treatment with corticosteroids is just as effective as

twice daily treatment.³ Furthermore, recent data also suggest that long-term disease control can be achieved by intermittent treatment with topical corticosteroids in combination with a moisturizer.⁴⁻⁶ However, corticosteroids and moisturizers may weaken the skin barrier function, with possible negative consequences for the eczema.⁷⁻¹⁰ Evidence to make recommendations on moisturizers is scarce and there is a need for more rigorous data on the preventive effectiveness of moisturizers.⁶ The majority of moisturizers on

the market are also cosmetics, which according to EU legislation cannot be recommended for treatment of skin diseases. The aim of the present study was to compare once and twice daily applications of a strong corticosteroid cream (betamethasone valerate 0.1%, BV) in addition to maintenance therapy with a 5% urea-containing moisturizer approved as a medicinal moisturizer. The degree of eczema was assessed by the patients and a physician. The scoring of eczema and the proportion of subjects showing clearance of eczema after 2 weeks of treatment were used to compare the efficacy of the treatments. Health-related quality of life (HRQoL) was also measured.

Materials and methods

The study was performed between October 2007 and May 2008 and was conducted in accordance with the Declaration of Helsinki and was approved by an Independent Ethics Committee and the national Competent Authority (Eudra CT 2007-002162-35). The patients (17 men and 27 women), mean age 46 years (range 22–76 years) had a clinically proven history of hand eczema and were recruited from a group of patients with a recent relapse of eczema at four out-patient clinics in Norway.¹¹ The study was explorative and a no sample size calculation was made.

The patients were randomized to using a strong corticosteroid cream BV (betamethasone valerate 0.1% cream, Betnoderm, ACO Hud AB) either twice daily (in the morning and in the evening) or once daily (in the evening). The treatment was double-blinded and combined with a moisturizer cream (M) (5% urea, Canoderm, ACO Hud AB, Sweden). All patients received two coded tubes; one for evening applications, labelled 'evening' and containing BV and one for morning applications, labelled 'morning' and containing either BV or M. The creams had a similar texture, were white and did not contain perfume. Furthermore, all patients received unblinded the moisturizing cream M (Canoderm) for additional treatment of their hands. The coded tubes were sequentially numbered according to a randomization list which was prepared and retained by the contract research organization. The participating clinicians included the patients and dispensed the tubes to the patients. The patients, the clinicians, those assessing the outcomes and those making the data analyses were blinded.

The patients were instructed to apply a thin layer of the creams on the affected areas for 2 weeks. After completing the study, the remaining medication was returned to the investigator for control weighing; treatment compliance was assessed by calculating the amount used and checking the notes on application in a patient diary.

Each patient judged the severity of their eczema daily on a 100 mm visual analogue scale (VAS), where 0 mm denoted no eczema and 100 mm extremely severe eczema. HRQoL was evaluated at inclusion and after 2 weeks using the Dermatology Life Quality Index (DLQI), which measures how much the patient's skin problem has affected his/her life over the past week.¹² This questionnaire consists of 10 questions and covers items such as

symptoms and feelings, leisure, daily activities, work and school. Each item is scored from 0 to 3, with higher scores indicating more problems. The questionnaire was available in Norwegian. The individual items are summed to generate an overall score, with a maximum possible score of 30. The investigator also scored the presence of eczema at inclusion and after 2 weeks using the Hand Eczema Extent Score (HEES). The HEES score is the sum of the scores of the two hands, and the maximum possible score is 74. Eczema on the entire dorsum of the hands scores 4, on part of the dorsum scores 2, on the entire palm scores 4 and on part of the palm scores 2; in addition, eczema on the dorsum, edge, volar part, fingertip, nail and web of the finger scores 1 for each part.¹ Clearance of hand eczema was defined as a score of ≤ 3 on the HEES in accordance with a previous study.¹³

The data are presented as summary statistics. The Wilcoxon–Mann–Whitney test was used to compare groups. The assessment of HEES was planned to be analysed using ANCOVA with the inclusion eczema score as a covariate. However, after the unblinding of the randomization codes but before the identity of the treatment groups was revealed, it was discovered that the distributional assumptions required for an ANCOVA were not met as more than half of the subjects at the end of the study had an eczema score of 0, the minimum value. Therefore, an additional analysis of this variable was performed where the subjects were split into two subgroups: subjects with eczema score values above and below the median value at inclusion. A value of $P < 0.05$ was considered statistically significant.

Results

All included participants received treatment and were analysed. Adherence to treatment was high. In both groups, the average numbers of applications in the morning and in the evening were between 13 and 14 of a possible 14. Similar amounts of creams were used in both groups; the total daily consumption was approximately 5 g (Table 1).

Both treatment groups improved their hand eczema scores (Fig. 1, Tables 2, 3, and 4). There were no significant differences between the two groups in the patients' scoring of degree of their hand eczema, when analysed with a repeated measures ANCOVA model ($P = 0.11$). The average reduction in VAS (mm) was 36.3 in the BV twice daily treatment group compared with 54.0 in the M + BV group (Table 2). The reduction was significant in both groups ($P < 0.001$).

The patients also considered their quality of life to have been improved by the treatments, as DLQI was reduced significantly ($P < 0.001$). There were no statistically significant differences in DLQI between the two groups after treatment when analysed with an ANCOVA model ($P = 0.27$; Table 3).

The clinicians scored significantly lower values of HEES after treatment for 2 weeks with M in the morning and BV in the evening, compared with BV twice daily ($P = 0.019$ by the exact Wilcoxon–Mann–Whitney test). In an attempt to adjust for HEES

Table 1 Daily use of study medication during the 2-week study

Estimated use per day (g)												
	BV twice daily						M + BV					
	<i>n</i>	Mean	SD	Min	Median	Max	<i>n</i>	Mean	SD	Min	Median	Max
Cream												
Morning	22	1.0	0.4	0.4	0.9	2.1	22	1.0	0.8	0.1	0.8	3.1
Evening	21	1.1	0.5	0.4	1.2	2.0	22	1.1	1.2	0.1	0.8	5.5
Moisturizer	22	3.1	1.9	0.0	2.9	7.2	22	2.8	2.0	0.2	2.6	6.5

BV, Betamethasone valerate; M, moisturizer.

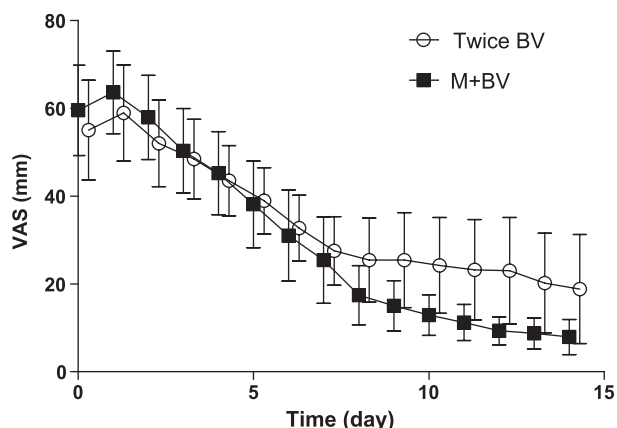


Figure 1 Eczema assessments on the visual analogue scale (VAS), recorded in patients' diaries, after treatment with betamethasone valerate (BV) twice daily or a moisturizer (M) in the morning and BV in the evening for 2 weeks. Mean values and 95% confidence intervals. *n* = 44.

values at inclusion, this variable was also analysed with subjects split into two subgroups: those with eczema score values below and above the median value at inclusion. For the group with

Table 2 Eczema assessment on the visual analogue scale (VAS), recorded in patients' diaries, at inclusion and after treatment with betamethasone valerate (BV) twice daily or a moisturizer (M) in the morning and BV in the evening for 2 weeks (*n* = 44)

Time, week	BV twice daily		M + BV	
	Mean (SD)	Min/median/max	Mean (SD)	Min/median/max
0	55.0 (25.6)	10/55/97	59.5 (23.2)	15/64/92
2	18.7 (28.9)	0/8/90	5.5 (6.1)	0/4/20
Change	-36.3 (36.0)	-97/-39/42	-54.0 (22.4)	-90/-61/-13

SD, standard deviation.

Table 3 Dermatology Life Quality Index (DLQI) at inclusion and after 2 weeks' treatment with betamethasone valerate (BV) twice daily or a moisturizer (M) in the morning and BV in the evening

Time, weeks	BV twice daily		M + BV	
	Mean (SD)	Min/median/max	Mean (SD)	Min/median/max
0	8.0 (5.2)	1/9/22	6.9 (4.1)	2/6/16
2	3.7 (5.7)	0/1/19	1.9 (1.9)	0/2/6
Change	-4.4 (4.8)	-13/-4/6	-5.0 (3.5)	-14/-4/-1

HEES values below the median value (i.e., HEES \leq 8), the exact version of the Wilcoxon–Mann–Whitney test gave a two-sided *P*-value of 0.023, indicating a significant difference in favour of the M + BV treatment group. In the group with HEES values above the median value (i.e., HEES $>$ 8), no such difference was seen (*P* = 0.514).

In total, 20 of the 22 patients (91%) on M + BV treatment were cleared of their eczema during the study, compared to 15 of the 22 patients (68%) on BV twice daily. The probability of achieving clearance with M + BV treatment was not significantly greater than with BV twice daily (*P* = 0.077). The odds ratio of achieving clearance was estimated at 4.67 (95% confidence interval 0.85–25.75).

Discussion

In this study, treatment adherence was high. The daily use of BV was approximately 1 g in the once daily group and 2 g in the twice daily group. Both groups improved significantly during the study period, but the twice daily treatment was not superior to the once daily. Common sense suggests that repeated applications of corticosteroids would produce substantially larger absorption and hence increased effect. However, our findings are in agreement with an experimental study on hydrocortisone¹⁴ and the

Table 4 Hand Eczema Extent Score (HEES) assessed by the clinician after treatment with betamethasone valerate (BV) twice daily or a moisturizer (M) in the morning and BV in the evening for 2 weeks

Time, week	BV twice daily (n = 22)		M + BV (n = 22)	
	Mean (SD)	Min/median/max	Mean (SD)	Min/median/max
0	15.1 (14.2)	4/8/54	11.4 (8.7)	2/9/38
2	2.5 (3.0)	0/2/10	0.9 (1.9)	0/0/8
Change	-12.5 (13.9)	-46/-8/2	-10.5 (9.0)	-38/-8/-2

conclusions on the effectiveness of once daily vs. more frequent applications of topical corticosteroids in clinical studies.³ Clinical studies do not generally show any advantage to more frequent application.³ The findings are also compatible with the skin penetration theory, which states that the concentration gradient of the active substance between the outside and the inside of the skin constitutes the driving force for penetration. As usually very small fractions of applied corticosteroids are absorbed by the skin during the first 24 h, more frequent application of a topical formulation will not necessarily increase the gradient and hence will not necessarily produce higher concentrations of the active substance deeper in the skin. Thus, the dosage on the skin can be seen as infinite, giving a fairly constant driving force for penetration throughout the day independent of application frequencies.

However, there are some confounding variables in the interpretation of application frequencies, the most obvious being the concomitant use of moisturizers. In this study, the once daily corticosteroid group used 4 g of moisturizer per day and the twice daily group used 3 g. Moisturizers are commonly used in conjunction with corticosteroids and this adjunctive therapy is considered to offer a steroid-sparing alternative to corticosteroids alone.^{15,16} However, moisturizers may not only change the absorption of the applied corticosteroids, but also have their own effect on the skin. The medicinal moisturizer used in this study has been shown in several studies to improve skin barrier function both in normal and in dry atopic skin.^{7,17-19} Application of moisturizers may also enhance the absorption of a previously applied drug, for example by solubilizing excess drug and thus making it available for absorption. Studies of placebo cream application following hydrocortisone dosing support this theory.²⁰

On the other hand, it is also possible that moisturizers decrease the absorption of the active ingredient, by diluting the remaining corticosteroid on the surface. A decreased exposure of the skin to corticosteroids could potentially promote normalization of the skin when the inflammation has subsided and the skin is recovering. The beneficial effects of corticosteroids in inflammatory skin conditions are well-known, but prolonged exposure of human epidermis to glucocorticoids results in cutaneous abnormalities. Corticosteroids reduce barrier lipid synthesis and the density of corneodesmosomes, which leads to an increased skin sensitivity and a weakened cutaneous permeability barrier homeostasis.²¹⁻²⁴ However, the urea-containing moisturizer in this study

may counteract these negative effects, as it has been shown to improve skin barrier function both in dry atopic skin^{17,18} and in normal skin.⁷ It was also recently found to upregulate the mRNA expression of peroxisome proliferator-activated receptor (PPAR) gamma in human skin.²⁵ A similar upregulation of PPAR gamma with a PPAR agonist (ciglitazone) has been found to improve permeability barrier homeostasis and to prevent several of the adverse effects observed from corticosteroid treatment in mice skin.²¹ Hence, moisturizers may have multiple effects on the skin and may also influence the efficacy of other topical medications.

In conclusion, this study confirms that twice daily use of corticosteroids is not superior to once daily use in treating eczema. On the contrary, the clinical assessment of HEES showed a larger benefit from once daily treatment with BV compared with BV twice daily, especially in the group of patients with a moderate eczema (HEES ≤ 8) at inclusion. These results suggest that after the initial suppression of the inflammation by BV treatment, further improvement of the skin barrier function by the use of a moisturizer is advantageous. Repairing an abnormal skin barrier function and preventing barrier dysfunction are among the most important strategies for reducing the risk of eczema.²⁶ This urea-containing moisturizer was recently also found to prevent relapse of flares in patients with controlled atopic eczema.^{11,27}

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