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INVESTIGATIVE REPORT

Effect of a Moisturizer on Skin Susceptibility to NiCl$_2$

CLAUS ZACHARIAE, ELISABETH HELD, JEANNE DUUS JOHANSEN, TORKIL MENNÉ and TOVE AGNER

Department of Dermatology, Gentofte University Hospital, Hellerup, Denmark

The aim of this study was to evaluate whether a moisturizer used on normal skin can increase skin response to allergens. Twelve nickel-allergic volunteers applied a lipid-rich moisturizer on the upper arm 3 times daily for 7 days, while the other upper arm served as a control. A control group followed the same treatment protocol. Following treatment with moisturizer, patch tests with 1% NiCl$_2$ aqueous solution were applied on each upper arm. After 24 and 72 h, skin reactions were evaluated blinded by clinical scoring, and by bioengineering methods measuring transepidermal water loss, skin colour and skin thickness. In the nickel-allergic group the strength of patch-test reactions was increased on the moisturizer-treated arm as evaluated by clinical scoring after 24 h and by measurement of transepidermal water loss and skin thickness after 72 h. In the control group, no significant differences were found. Our findings show that threshold values for elicitation of allergic reactions in already sensitized individuals may be influenced by use of lipid-rich moisturizers. *Key words: Bioengineering methods; nickel-allergy; threshold values.*

Claus Zachariae, Department of Dermatology, Gentofte University Hospital, Niels Andersensvej 65, DK-2900 Hellerup, Denmark. E-mail: cz@dadlnet.dk

Moisturizers are commonly used as a protective measure during working hours in wet occupations or as after-work emollients. The protective effect of a moisturizer in these situations is well recognized and documented (1, 2). It is also well recognized that use of moisturizers on eczematous skin has a positive influence on skin barrier function (1, 3, 4), and a standardized method for evaluation of the effect of topical formulations on irritation has been proposed (5). However, moisturizers are increasingly commonly used on normal skin for cosmetic reasons to alleviate subjectively dry skin or as a cultural phenomenon encouraged by advertisements from the cosmetic industry. Recently, some attention has been given to this, as previous studies have indicated that using moisturizers on normal skin may increase skin reactivity to irritants such as sodium lauryl sulphate (SLS) (6, 7). When skin is hydrated following use of moisturizers, it may become more permeable to hazardous substances, leading to an increased skin susceptibility to irritants.

Theoretically, also the penetration of allergens may be facilitated, and the threshold value for eliciting allergic skin reactions in already sensitized individuals may be lowered.

The aim of our study was to evaluate whether regular use of a moisturizer on normal skin can influence the response of the skin to challenge allergens in already sensitized individuals.

MATERIALS AND METHODS

Participants

Twelve Caucasian volunteers with known nickel allergy (all females; mean age 24.4 years, range 20–28) were included in the study. An inclusion criterion for the study was a positive patch test to nickel within the past 2 years, or a history of persistent reactions to nickel in metal alloys within the same period. Subjects with current contact dermatitis or atopic eczema were excluded. Ten healthy volunteers (3 females and 7 males; mean age 33.4 years, range 27–45) without nickel allergy were included as a control group. Written informed consent was obtained from all the volunteers, and the local ethics committee approved the study.

Materials

Moisturizer. A moisturizer with a high lipid content (70%): Locobase®, (Yamanouchi Pharma, Leiderdorp) was applied 3 times daily for 7 days prior to allergy challenge. The participants were not allowed to use any other moisturizer on the arms 7 days prior to entering the study. Each participant was given a supply of 50 g of the moisturizer and a checklist for daily recording of the treatment.

Nickel patch test. Two patch tests, one on each arm (large Finn Chambers, diameter 12 mm, Epitest, Helsinki, Finland), with 50 µl of an aqueous 1% NiCl$_2$ solution on a filter disc were applied symmetrically on the ventral side of the upper arm. Two empty chambers, one on each arm, were applied as controls.

Methods

Prior to the study, electrical capacitance (see below) was measured on each upper arm. The volunteers in both groups were then randomized to have the ventral aspect of either the left or the right upper arm treated with moisturizer, 3 times daily for the following 7 days. The other arm served as a symmetrical control. The investigator was blinded to the randomization code. After 7 days the treatment was stopped, and electrical capacitance was measured again the following day. Baseline values for transepidermal water loss (TEWL), skin colour and skin thickness were measured on two areas on the ventral aspect of each upper arm, and patches were applied. The patch tests were removed after 24 h (day 1), and clinical scoring and measurements for TEWL, skin colour and dermal thickness

were performed on days 1 and 3 (24 h and 72 h). Clinical scoring was performed according to the Guidelines from ICDRG (8).

The following bioengineering measurements were performed:

Electrical capacitance was measured as an indicator of the hydration state of the skin using a Corneometer® CM820 (GMBH, Köln, Germany) (9). Measurements were taken before the start of moisturizer treatment and one day after the treatment ended, as the mean of 3 measurements for each arm.

Transepidermal water loss (TEWL) was measured with an Evaporimeter (Servo Med, Stockholm, Sweden) and served as an indicator of the integrity of the skin barrier function. The measurements were performed according to the Guidelines for TEWL established by the European Society of Contact Dermatitis (ESCD) (10). The values were calculated as the mean of 2 measurements.

Skin colour was evaluated with a Minolta Chroma Meter CR-300. The colour is expressed in a 3-dimensional coordinate system (L*a*b*). Redness of the skin is measured on the a* colour coordinate, which is an indicator of the presence of haemoglobin reflecting the level of inflammation in the skin (11). The values were calculated as the mean of 3 measurements.

Skin thickness was measured by echographic evaluation using a 20-MHz ultrasound system (Dermascan C; Cortex Technology, Hadsund, Denmark), which supplies false-colour images representing a cross-section of the skin (12). The measurements were performed according to the manufacturer's manual as A-mode scans. The probe was coupled on the skin over a water path, a membrane and a jelly layer. The evaluation was performed as the mean of duplicate measurements.

Statistics

Paired statistical tests were used to compare moisturizer-treated arms with untreated symmetrical controls. Student's *t*-test was used for bioengineering measurement data, as data followed a normal distribution. The Wilcoxon signed rank test was used for clinical scoring. The Shapiro-Wilk test was used to test for normal distribution. All calculations were done using SPSS 8.0 for Windows. A significance level of $p < 0.05$ was chosen.

RESULTS

After one week's treatment with moisturizer the hydration level, as measured by electrical capacitance, was statistically significantly increased on the treated arm compared with the non-treated arm for both the nickel-allergic group ($p < 0.0001$) and the control group ($p < 0.0001$).

Clinical scoring

All subjects in the nickel-allergic group had a positive reaction to NiCl$_2$ after either 24 h or 72 h (day 1 or 3). Four subjects had a doubtful positive reaction only. Patch-test reactions are listed in Table I. A statistically significant increased reaction to NiCl$_2$ was found on the moisturizer-treated arm as compared to non-treated arm on day 1 ($p = 0.01$), but not on day 3 ($p = 0.27$). In the control group without nickel allergy, one subject had a doubtful reaction to nickel after 72 h. This person had no

Table I. *Clinical scoring of patch-test reactions to NiCl$_2$ after 24 h and 72 h (Days 1 and 3) on moisturizer-treated arm and non-treated arm. A statistically significant increased reaction to NiCl$_2$ was found on the moisturizer-treated arm as compared to the non-treated arm on Day 1, but not on Day 3.*

Subject	24 h (Day 1)		72 h (Day 3)	
	+cream	−cream	+cream	−cream
1	+ + +	+ +	+	+?
2	+	+?	+?	0
3	0	0	0	+?
4	+?	0	+?	0
5	+ +	+	+ +	+ +
6	+	+	+?	+?
7	+?	+?	+	+?
8	0	0	0	+?
9	+ +	+	+ +	+ +
10	+?	0	+?	0
11	+	+	+ +	+ +
12	+	+	+?	+?
	$p = 0.012$		$p = 0.274$	

history of metal rash, but had been ear-pierced. Nickel allergy was suspected, but further patch testing with nickel was refused, and the subject was excluded from the study.

TEWL

No significant differences were found in baseline values obtained from moisturizer-treated and non-treated arms. Skin response after 24 h and 72 h (days 1 and 3) were calculated as the delta value between NiCl$_2$ and the empty chamber on the treated arm as compared to delta value on the non-treated arm. After 24 h the difference was not statistically significant. Data at 72 h are presented in Fig. 1. A statistically significant increased skin response as evaluated by TEWL measurement was found on the moisturizer-treated arm compared to the non-treated arm after 72 h ($p = 0.04$). No significant difference in skin reactivity to nickel between moisturizer-treated and non-treated arms was found in the control group, as evaluated by TEWL measurements.

Skin colour

No significant difference was found in baseline values obtained from moisturizer-treated and non-treated arms. Skin response after 24 h and 72 h (days 1 and 3) were calculated as the delta value between NiCl$_2$ and the empty chamber on the treated arm as compared to delta value on the non-treated arm. After 24 h, the difference was not statistically significant. Data at 72 h are given in Fig. 2. Although not statistically significant, a trend towards an increased skin response as evaluated by colorimetry was found on the moisturizer-treated arm compared to the non-treated arm after 72 h ($p = 0.06$). No significant
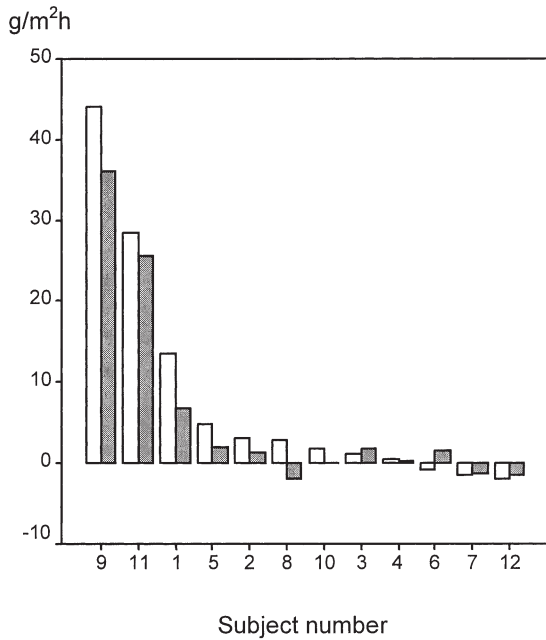
Fig. 1. Delta transepidermal water loss (TEWL) values (NiCl$_2$ patch – empty patch) on the moisturizer-treated arm (□) and the non-treated arm (■) at 72 h. Skin response was statistically significantly increased on the treated arm as compared to the non-treated arm ($p = 0.04$).
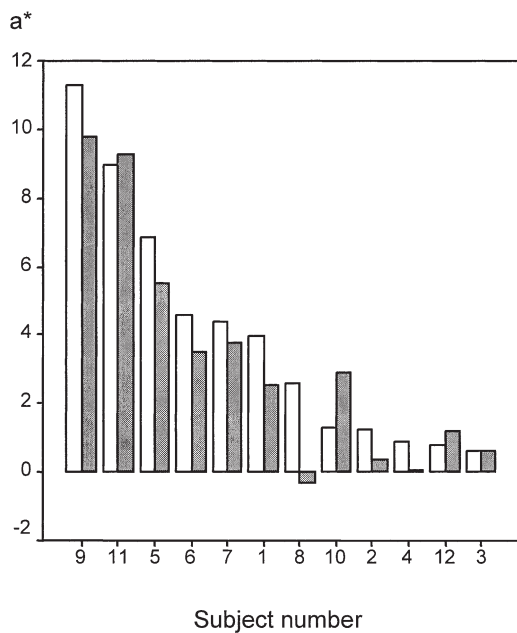

Fig. 2. Delta skin colour a* values (NiCl$_2$ patch – empty patch) on moisturizer-treated arm (□) and non-treated arm (■) at 72 hours. Skin response was increased, although not statistically significant, on the treated arm as compared to the non-treated arm ($p = 0.06$).

difference in skin reactivity to nickel between the moisturizer-treated arm and the non-treated arm was found in the control group, as evaluated by skin colour measurements.

Skin thickness

No significant difference was found in baseline values obtained from the moisturizer-treated and non-treated arms. Skin response after 24 and 72 h (days 1 and 3) were calculated as the delta value between NiCl$_2$ and the empty chamber on the treated arm as compared to the delta value on the non-treated arm. After 24 h, the difference was not statistically significant. Data at 72 h are presented in Fig. 3. A statistically significant increased skin response as evaluated by ultrasound measurement was found on the moisturizer-treated arm as compared to the non-treated arm after 72 h ($p = 0.006$). No significant difference in skin reactivity to nickel between the moisturizer-treated and non-treated arms was found in the control group, as evaluated by measurement of skin thickness (Fig. 4).

DISCUSSION

The results reveal an increased skin response to NiCl$_2$ in nickel-sensitized individuals, when NiCl$_2$ is applied as a patch test on normal skin, which has been treated with a lipid-rich moisturizer for one week.

The valuable effect of moisturizers when used on eczematous skin and skin with impaired barrier function should not be doubted, and has been confirmed in a number of experimental studies (1 – 3, 5). In a number of field studies testing after-work emollients/moisturizers, a positive effect has been shown on skin irritation (13 – 15), while other studies have not been able to confirm this effect (16). Positive effects of moisturizers used as barrier creams before or during working hours have also been shown for selected irritants (17, 18). It would be highly
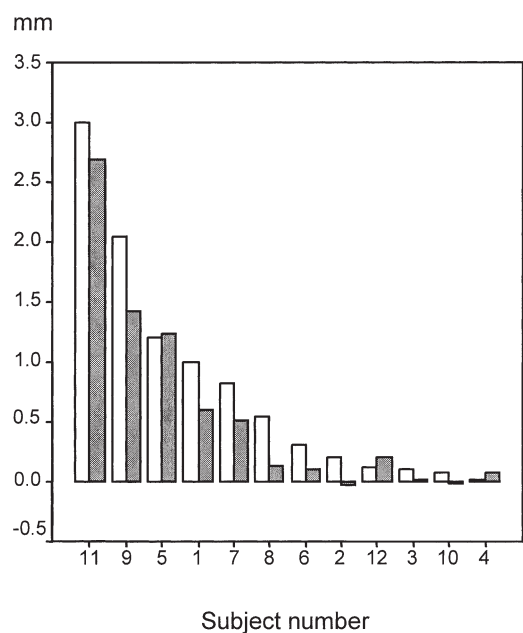

Fig. 3. Delta skin thickness (mm) (NiCl$_2$ patch – empty patch) on moisturizer-treated arm (□) and non-treated arm (■) at 72 h. Skin response was statistically significantly increased on the treated arm as compared to the non-treated arm ($p = 0.006$).
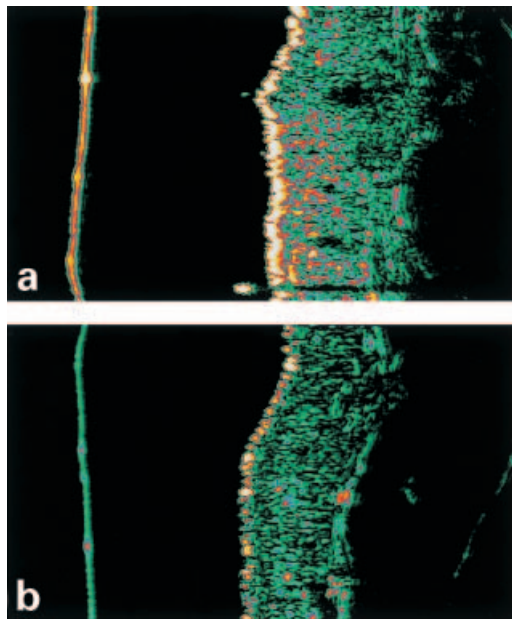
Fig. 4. 20-MHz ultrasound of the skin of subject number 8 at 72 h after patch tests with 1% NiCl$_2$ aqueous solution. (*a*) The moisturizer-treated arm. (*b*) The non-treated arm.

interesting in a future study to examine whether the treatment of chronic eczematous skin with a moisturizer shortly before contact with an allergen also enhances allergic reaction to nickel ions. This may, however, not be the case, since treatment of chronic eczema with a moisturizer will improve the skin barrier function, and this way round at least theoretically diminish the penetration of nickel.

However, the positive effect of moisturizers when used on normal skin has been questioned, and an increased skin susceptibility to irritants following use of moisturizers on normal skin has been demonstrated in experimental studies (6, 7). The present results indicate that application of moisturizers on normal skin may also influence the threshold value at which an allergic contact reaction to NiCl$_2$ can be elicited.

Regular application of a moisturizer on the skin is well known to cause an increased skin hydration, reaching a plateau level after 3–5 days (6). In the present study an increase in electrical capacitance after 7 days on the treated arm indicates increased skin hydration, and confirms that application of a moisturizer has been completed. NiCl$_2$ was preferred to NiSO$_4$ for patch testing because of its increased penetration ability, and an aqueous solution of nickel was chosen since application of nickel in petrolatum might have influenced barrier properties and levelled out the difference between treated and non-treated skin.

A low concentration of NiCl$_2$ was chosen to make grading of the reactions easier, and because of this, some subjects had only a doubtful positive reaction to NiCl$_2$. However, an increase in NiCl$_2$ concentration to more than 1% when using large Finn chambers may cause irritant

skin reactions. To ensure that the increased response to NiCl$_2$ following moisturizer treatment was an increased allergic and not an increased irritant response, a control group without nickel allergy was included. In this group no significant differences between the moisturizer-treated and non-treated arms were found with respect to skin reactivity to NiCl$_2$.

The increased skin response to nickel on the moisturizer-treated arm was statistically confirmed after 24 h by clinical scoring only. After 72 h, which is generally accepted as an ideal time-point to evaluate patch-test reaction (19), a significantly increased skin response was found on treated skin as evaluated by measurement of TEWL and skin thickness. Clinical scoring as well as measurement of skin colour showed the same tendency. The relatively small number of participants in the study could explain the lack of statistical significance for skin colour values ($p = 0.06$), since this method has previously been shown to be slightly less sensitive than TEWL and skin-thickness measurements for evaluation of some patch-test reactions (20). Although statistical significance was not obtained at the same time for clinical scoring and instrumental measurements, all evaluations pointed in the same direction. While skin thickness and skin colour reflect the inflammatory reaction caused by the patch test, TEWL reflects skin barrier impairment subsequent to the inflammation (21).

When the hydration state of the stratum corneum is increased, it becomes more permeable to hydrophilic substances. A high level of hydration of the stratum corneum may facilitate transportation of a hydrophil allergen, and this is likely to be positively related to the amount of lipids in the moisturizer. A positive relationship between the amount of lipids and the effect on skin barrier function has been reported (4). Although our results in this present study clearly indicate increased allergic response to nickel after moisturizer treatment, the conclusions are limited to moisturizers with a high lipid content and nickel in aqueous solution, as less lipid-rich moisturizers and response to other allergens may give a different or less clear result.

The perspectives of the findings are interesting with respect to occupational contact dermatitis as well as contact dermatitis related to consumer products. Advising employees in risk occupations for hand eczema on the use of moisturizers is likely to be much more complicated than is generally assumed. It may also have important practical consequences for determination of threshold values and the risk assessment for contact allergens in industrial and consumer products, since our results show that threshold values for elicitation of allergic reactions in nickel-sensitized individuals are influenced by use of lipid-rich moisturizers.

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