

Topical Corticosteroids in the Treatment of Acute Sunburn

A Randomized, Double-blind Clinical Trial

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Objective: To examine the effect of topical corticosteroid treatment on acute sunburn.

Design: Randomized, double-blind clinical trial.

Setting: University dermatology department.

Patients: Twenty healthy volunteers with Fitzpatrick skin types I (highly sensitive, always burns easily, tans minimally) through III (sun-sensitive skin, sometimes burns, slowly tans to light brown).

Intervention: Seven 34-cm² areas were marked on the upper aspect of the back of each participant. An untreated area was tested to determine UV sensitivity. Two areas were treated with excess amounts (2 mg/cm²) of either a moderate-potency corticosteroid or a high-potency corticosteroid 30 minutes before UV-B exposure as controls. Six or 23 hours after exposure to radiation, the remaining areas were treated with the 2 corticosteroid preparations.

Main Outcome Measures: The sunburn improvement factor (SIF) was determined by the following equation: SIF = MED (minimal erythema dose) on treated skin/

MED on nontreated skin. An SIF greater than 1 indicated an effect of topical corticosteroids in sunburn relief.

Results: The SIFs in the areas treated with either topical corticosteroid 30 minutes before UV-B exposure or high-potency corticosteroid 6 hours after UV-B exposure were significantly different from SIFs in areas that received no treatment (SIF 1.1-1.7; $P < .05$). Only the median SIF of 1.7 in the areas treated with high-potency corticosteroid 30 minutes before UV-B exposure was clinically relevant. The areas treated 23 hours after UV-B exposure and the areas treated with a moderate-potency corticosteroid 6 hours after UV-B exposure showed no significant reduction in redness.

Conclusion: Treatment with topical moderate-potency or high-potency corticosteroids does not provide a clinically useful decrease in the acute sunburn reaction when applied 6 or 23 hours after UV exposure.

Clinical Trial Registry: clinicaltrials.gov Identifier: NCT00206882

Arch Dermatol. 2008;144(5):620-624

SUNBURN IS THE CLINICAL MANIFESTATION of a complex inflammatory process in the skin, most commonly encountered in fair-skinned populations. Shortwave UV radiation (UV-B, 280-320 nm) from sunlight is the main cause of sunburn. UV-B is absorbed by DNA and causes formation of DNA lesions such as cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts, leading to an inflammatory reaction with vasodilation and increased vascular permeability.¹ Moreover, UV-B increases the production of free arachidonic acid from the cell membrane, which results in increased prostaglandin E₂ synthesis, also involved in the formation of UV-induced erythema.²

Clinically, erythema develops gradually 3 to 5 hours after sun exposure,

reaching a maximum at 12 to 24 hours, and may persist for more than 48 hours before slowly fading.³ The symptoms range from mild redness to painful erythema with edema and blistering. In worst cases, severe sunburn may result in systemic reactions such as fever, chills, and dehydration.

Current therapeutic options are based on management of the symptoms; topical corticosteroids are usually first-line treatment. The efficacy of topical corticosteroids is controversial.⁴ One study has shown a lower sunburn reaction on days 4 and 5 after application of moderate-potency corticosteroids twice a day starting 6 hours after exposure to radiation.⁵

It is crucial to patients that any treatment offer a substantial anti-inflammatory effect and, thereby, relief of symp-

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toms within the first day. In practice, treatment of sunburn is started at the earliest 6 hours after sun exposure or the next day. We conducted this randomized, double-blind, controlled clinical trial to provide evidence for the acute effects of moderate-potency and high-potency topical corticosteroids on the treatment of sunburn when applied 6 or 23 hours after UV-B exposure.

METHODS

SUBJECTS

Twenty healthy volunteers (16 women and 4 men; age range, 23-62 years) were recruited through advertising. Only individuals with Fitzpatrick skin types I (highly sensitive, always burns, never tans) through III (sun-sensitive skin, sometimes burns, slowly tans to light brown) were included.⁶ Pregnant and lactating women were excluded from the trial. Exposure to sun or solarium was not allowed in the 4 weeks preceding the study and during the study. Approval was obtained from the Copenhagen Ethics Committee (KF 01-272662), and the study was performed according to the principles of the Declaration of Helsinki. All participants agreed to take part in the trial after receiving oral and written information.

TREATMENT

Six 34-cm² areas were marked on the upper aspect of the back of each participant. The location of the areas was randomized by lot of computer-generated schemes to avert any area effect. The areas were treated with excess amounts (2 mg/cm²) of either a moderate-potency corticosteroid (hydrocortisone-17-butyrate [Locoid]; Yamanouchi Europe BV, Leiderdorp, the Netherlands) or a high-potency corticosteroid (clobetasol propionate [Dermovate]; Glaxo Wellcome, Barnard Castle, England). For each corticosteroid, 1 area was treated 30 minutes before UV-B exposure as a control. Six hours after UV-B exposure, 2 areas were treated with either the moderate-potency corticosteroid or the high-potency corticosteroid. A similar treatment was conducted on the remaining 2 areas after 23 hours. Both the observer (A.F.) and the patient were blinded to whether a moderate-potency or a high-potency corticosteroid was applied.

RADIATION SOURCE AND PROCEDURE

The UV source was a bank of TL12 fluorescent tubes (Koninklijke Philips NV, Eindhoven, the Netherlands) emitting broad-band UV-B (emission spectrum, 280-350 nm; peak emission, 313 nm), and the exposure was conducted at a distance of 50 cm. Irradiance was measured with a UV spectroradiometer (Solar Hazard; Solatell, 4D Controls Ltd, Cornwall, England). The calibration of this equipment is traceable to the National Physical Laboratory of the United Kingdom. One phototest was conducted in each corticosteroid-treated area using a minimal erythema dose (MED) template (MED Test Patch, ChromoLight APS, Copenhagen, Denmark) lying directly on the skin. The MED test patch has 6 windows measuring 1.2 × 1.2 cm each, which allows UV radiation to pass through with a dose increment of 25%. A test of the transmission in the windows was performed using a radiometer equipped with a standard erythema dose (SED) detector (IL1700 and SED 240, respectively; International Light Technologies Inc, Newburyport, Massachusetts). The dose transmitted was used to calculate the sun improvement factor (SIF) as described below. We quantified all UV doses in SED (standard erythema dose, 10 mJ/cm² at 298 nm, using the erythema action spectrum of the International

Commission on Illumination).⁷ An untreated area was phototested 1 day in advance to determine the UV dose needed to produce just-perceptible erythema. The induced erythema was graded visually 1 hour after the last application of corticosteroid, that is, 24 hours after UV-B exposure, according to an established 5-point scale (0 indicates no difference from surrounding skin; [+], just-perceptible erythema; +, uniform erythema with sharply defined borders; ++, bright red with slight induration [edema] on palpation; and +++, bright red and pronounced induration [edema] raised above the surrounding skin). The dose to just-perceptible erythema reaction was used as the MED because it can be determined with the best precision.⁸ If application of topical corticosteroids was effective in reducing the sunburn reaction, the erythema reaction would be less pronounced in the corticosteroid treated areas compared with the control area. We, therefore, decided to calculate the SIF because this would quantify the degree of suppression. The SIF was determined using the following equation: SIF = MED on treated skin/MED on nontreated skin. Thus, an SIF of more than 1 indicates an effect of topical corticosteroids in sunburn relief.

DATA ANALYSIS

$P < .05$ was considered statistically significant. Not all data were normally distributed and were, therefore, analyzed using the Wilcoxon signed rank test and the Mann-Whitney test. Commercially available software was used to analyze these data (GraphPad Prism, version 4.03; GraphPad Software, Inc, San Diego, California).

RESULTS

The median SIFs obtained in the different areas are given in the **Table**, and the scatter plots in **Figure 1** illustrate the results. The back of a volunteer is shown 23 hours after exposure to UV-B in **Figure 2**.

The SIFs in areas treated with corticosteroid 30 minutes before UV-B exposure and the areas treated with high-potency corticosteroid 6 hours after UV-B exposure were significantly different from SIFs in areas that received no treatment ($P < .05$). However, only the median SIF of 1.7 found in the areas treated with high-potency corticosteroid 30 minutes before UV-B exposure was clinically relevant because the median SIF of 1.1 in the other 2 areas cannot be considered clinically relevant (Table). No significant SIF was found in the areas treated with corticosteroid 23 hours after UV-B exposure or in the areas treated with a moderate-potency corticosteroid after 6 hours. The erythema reactions more pronounced than the just-perceptible reaction showed a similar response to treatment with corticosteroids as the just-perceptible reaction (Table). However, the reduction in redness showed a tendency to be stronger for the lower erythema reaction in the areas treated before UV-B exposure, although no significant difference was found when comparing the erythema reactions.

COMMENT

Treatment with topical moderate-potency or high-potency corticosteroids does not decrease the acute sunburn reaction when applied 6 or 23 hours after UV-B ex-

Table. Sunburn Improvement Factor in Areas Treated With a Moderate-Potency (Hydrocortisone-17-Butyrate) or a High-Potency (Clobetasol) Corticosteroid 30 Minutes Before and 6 and 24 Hours After UV-B Exposure

Treatment Time	Erythema Reaction	Hydrocortisone-17-butyrate, Median (IQ Range)	Clobetasol Propionate, Median (IQ Range)	No. of Participants
30 min Before UV-B exposure	(+)	1.1 ^a (1.0-1.4)	1.7 ^a (1.6-1.9)	20
	+	1.2 ^a (1.0-1.4)	1.6 ^a (1.4-2.0)	17, 16 ^b
	++	1.1 (0.8-1.4)	1.3 (1.2-1.7)	10, 5 ^b
6 h After UV-B exposure	(+)	1.0 (0.9-1.1)	1.1 ^a (1.0-1.3)	20
	+	1.0 (0.8-1.3)	1.1 ^a (0.9-1.4)	17
	++	1.1 (1.0-1.3)	1.1 (1.0-1.3)	12, 10 ^b
23 h After UV-B exposure	(+)	0.9 (0.8-1.0)	1.0 (0.9-1.2)	20
	+	0.9 (0.8-1.1)	1.0 (0.8-1.2)	17
	++	1.0 (0.9-1.1)	1.0 (1.0-1.1)	13

Abbreviations: IQ, interquartile; (+), just perceptible; +, uniform erythema with sharply defined borders; ++, bright red with slight induration (edema) on palpation.

^a $P < .05$.

^bThe first value is for hydrocortisone-17-butyrate; the second, for clobetasol propionate.

posure. This is independent of the degree of erythema from just perceptible to severe. We used an amount of 2 mg/cm² as recommended for sunscreens, which is a much higher quantity than generally applied. The subjects were not treated for a longer period because the purpose of applying the corticosteroids was the immediate suppression and relief of the painful sunburn with a lasting reduction in redness. Data from an earlier study, however, indicate that the recovery time may be reduced slightly when using topical corticosteroids twice a day starting 6 hours after UV-B exposure, but the effect was not found before day 4 or 5.⁵

The vasoconstriction achieved with topical corticosteroids is believed to result in immediate reduction in redness and discomfort of sunburn. In our study, both just perceptible and severe erythema treated with corticosteroids 6 and 23 hours after UV-B exposure was, however, similar to untreated skin when scored 1 or 18 hours after application of corticosteroids, indicating no effect on vasoconstriction at these time points. To assess the potency of topically applied corticosteroids, the vasoconstrictor assay that was originally proposed by McKenzie and Stoughton⁹ and since modified by the US Food and Drug Administration¹⁰ has been used widely. The degree of vasoconstriction on normal, unirradiated skin is measured at different time points and reaches a maximum within 6 to 16 hours after application, followed by a slow decrease.¹¹ It should, thus, be possible to detect an effect at least when evaluated 18 hours after treatment.

Corticosteroids diffuse readily across the cell membranes and bind to their intracytoplasmic receptor that translocates to the nucleus. Here they bind to glucocorticoid response elements in the promoter region of corticosteroid-sensitive genes. This leads to upregulation of several anti-inflammatory proteins such as lipocortin-1 (phospholipase A₂ inhibitor), nuclear factor- κ B inhibitor, and mitogen-activated protein kinase phosphatase-1, whereas the transcription of proinflammatory proteins including phospholipase A₂ and cyclooxygenase-2 is suppressed.¹² The receptor complex may also bind directly to coactivator proteins and inhibit the function of other transcription factors including nuclear factor- κ B

and activator protein-1, which is crucially involved in the inflammatory response.

A possible explanation for the lack of effect of applying corticosteroids after sunburn formation may be that the cellular functions are so severely disturbed by the heavy dose of UV radiation that the corticosteroids are unable to bind to their intracytoplasmic receptor and conduct these actions. A second possibility is that the vasoconstriction is counteracted by nitric oxide produced by the skin cells in response to UV-B exposure, which causes the vasodilation and erythema.¹³ Nitric oxide and prostaglandin E₂ are mediators of UV-induced erythema, with continuous synthesis of nitric oxide throughout the course of UV-induced vasodilation.² However, it has been described that nitric oxide is responsible for the erythema at low doses and that prostaglandin E₂ has a progressively more important role when the UV-B dose is increased. Thus, indomethacin, an inhibitor of cyclooxygenase, had no effect on the MED reaction but substantially reduced erythema after 2 and 4 times the MED when applied under plastic film occlusion for 3 hours.² Inasmuch as corticosteroids also inhibit cyclooxygenase and, in addition, phospholipase A₂, which both participate in the conversion of arachidonic acid to prostaglandin E₂, the same may apply to corticosteroids. Although our study focused primarily on the effect on the MED reaction because this degree of erythema can be determined with the best precision, we also evaluated the effect on the appearance of erythema caused by 2 higher degrees of erythema. Not all of the participants developed erythema reactions more severe than the MED reaction, and the number of patients was, therefore, fewer (Table). However, we could not confirm an effect of corticosteroids on more severe erythema, indicating that a single application of corticosteroid after 6 or 23 hours does not provide a clinically useful reduction of the sunburn reaction regardless of severity. The effect of indomethacin treatment may be a result of the use of a plastic occlusion. Similarly, the effect of corticosteroids may be increased when applying them under occlusion. We did not use corticosteroids under occlusion because this is not usual clinical practice.

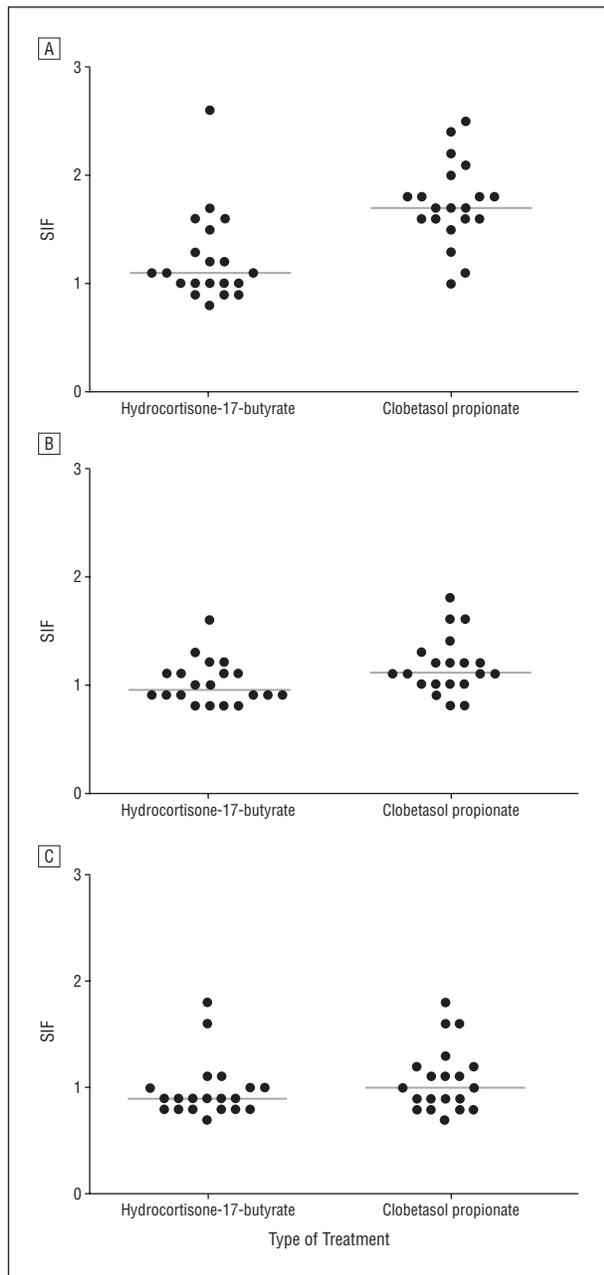


Figure 1. Scatter plots show the effect of applying moderate-potency corticosteroids (hydrocortisone-17-butyrate [H]) and high-potency corticosteroids (clobetasol propionate [C]) before (A), 6 hours after (B), and 23 hours after (C) UV-B exposure. SIF indicates sunburn improvement factor.

One of the first cytokines released in the initial inflammatory reaction is tumor necrosis factor- α . Tumor necrosis factor- α is increased 4 hours after solar-simulated radiation in human skin, reaching a maximum at 15 hours.¹⁴ When patients are treated for sunburn, typically 6 to 24 hours after exposure, the inflammatory process has begun and developed substantially at the molecular level. It is, therefore, conceivable that application of corticosteroids 6 to 24 hours after exposure to UV radiation might have only a slight effect on the inflammation, whereas application of corticosteroids before exposure to radiation would result in more pronounced inhibition of the inflam-

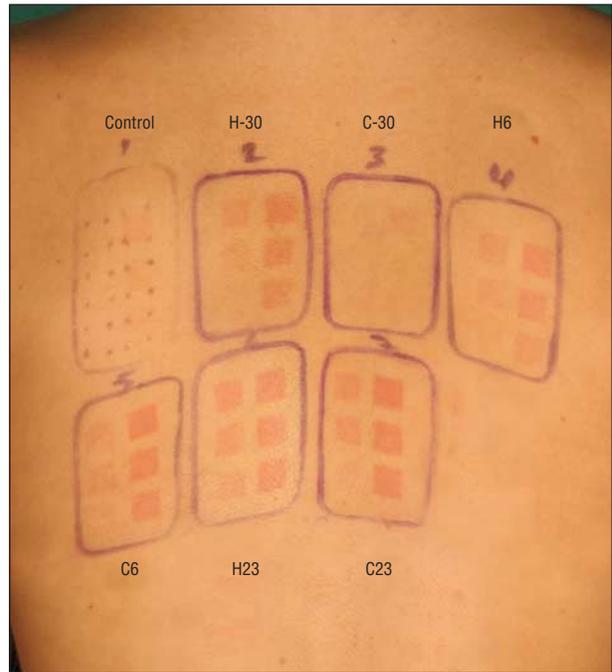


Figure 2. The back of a volunteer 24 hours after UV-B exposure. The control area was treated 1 day before the other areas to determine the dose needed to produce just-perceptible erythema, and the reaction has faded. The corticosteroid-treated areas were treated either with hydrocortisone-17-butyrate (H), a moderate-potency corticosteroid, or clobetasol propionate (C), a high-potency corticosteroid. The time of application was 30 minutes before (-30), 6 hours after (6), or 23 hours after (23) UV-B exposure. Redness was significantly reduced only in the area treated with a high-potency corticosteroid 30 minutes before UV-B exposure (sun improvement factor 1.7). The sun improvement factor in all other areas did not exceed 1.1, and the erythematous area was, thus, not different from untreated skin.

mation. In accord with this, erythema in the control area treated with high-potency corticosteroid before exposure to UV radiation was significantly reduced compared with erythema on untreated skin, whereas we were unable to detect a clinical effect of corticosteroids applied 6 and 23 hours after UV-B exposure.

The use of a high-potency corticosteroid before UV-B exposure suppressed erythema formation corresponding to an SIF of 1.7. This indicates that patients who have, for example, eczema and are treated with corticosteroids are not at higher risk of sunburn than other individuals. The patients may possibly obtain some sun protection from their treatment because an SIF of 1.7 is not negligible compared with other means of photoprotection. The MED after 10 solarium sessions increases, with about 50% corresponding to an SIF of 1.5.¹⁵

Accepted for Publication: August 11, 2007.

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Author Contributions: Dr Faurschou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Faurschou and Wulf. *Acquisition of data:* Faurschou. *Analysis and interpretation of data:* Faurschou and Wulf. *Drafting of the manuscript:*

Faurschou. *Critical revision of the manuscript for important intellectual content*: Faurschou and Wulf. *Statistical analysis*: Faurschou. *Obtained funding*: Wulf. *Administrative, technical, or material support*: Wulf. *Study supervision*: Wulf.

Financial Disclosure: None reported.

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