

Does Order of Application of Emollient and Topical Corticosteroids Make a Difference in the Severity of Atopic Eczema in Children?

Su Yuen Ng, M.B.B.S.,* Sabeera Begum, M.Paeds. (UM),* and Sze Yee Chong, M.Paeds. (UM)†

*Paediatrics, Institut Pediatrik, Hospital Kuala Lumpur, Jalan Pahang, Kuala Lumpur, Wilayah Persekutuan, Malaysia, †Paediatrics, Hospital Selayang, Selayang, Selangor, Malaysia

Abstract:

Background: Atopic eczema (AE) is a common chronic inflammatory skin disorder in children, with emollients and topical corticosteroids (TCSs) commonly prescribed as treatment. There is no published guidance on the correct order of application of emollient and TCS in children with AE.

Objective: The objective of this study was to determine whether the order of application of emollient and TCS makes a difference in the severity of AE in children.

Methods: Forty-six patients ages 4 months to 5 years with moderate to severe AE were randomized to two groups: group A applied emollient followed by TCS 15 minutes later twice daily, and group B applied TCS followed by emollient 15 minutes later twice daily for 2 weeks.

Results: There was no statistically significant difference in the Eczema Area and Severity Index (EASI) score, percentage of body surface area (BSA) affected, or itch score between groups A and B ($p > 0.05$). Group A had statistically significant improvement in the EASI score, percentage BSA affected, and itch score from baseline to weeks 1 and 2; group B demonstrated statistically significant improvement only in the EASI score from baseline to week 1 and in itch score from baseline to week 2. There was no difference in adverse events between the groups.

Conclusion: This study suggests that the order of application of emollient and TCS does not matter in the treatment of AE in children and that parents can apply topical medications in whichever order they prefer.

Atopic eczema (AE) is a common chronic, inflammatory, pruritic skin disorder in children that often occurs in families with other atopic diseases (1). No

guidance has been published on the correct order of application of emollient and topical corticosteroid (TCS) in children with atopic eczema. There is some

Address correspondence to Su Yuen Ng, M.B.B.S., Paediatrics, Institut Pediatrik, Hospital Kuala Lumpur Jalan Pahang, 50586, Kuala Lumpur, Wilayah Persekutuan, Malaysia, or e-mail: ngsy2002@yahoo.com.

evidence that well-moisturized skin requires less TCS. A study of 173 infants younger than 12 months showed that emollients significantly reduced the amount of high-potency TCS needed to control AE (2).

The National Institute for Health and Clinical Excellence (NICE) has identified the order and timing of the application of emollient as an important research priority (3), so this study was conducted to determine whether the order of application of emollient and TCS makes a difference in the severity of AE in children and, if so, the correct order of application.

MATERIALS AND METHODS

Study Population

The study population consisted of children ages 4 months to 5 years diagnosed with moderate to severe AE for whom written consent was obtained. Diagnosis was according to the Hanifin and Rajka modified (UK) diagnostic criteria (4), and severity was assessed according to the Rajka and Langeland criteria (5). Exclusion criteria included patients whose parents or caregivers were unable to apply the topical medications; patients with other skin disease in the study area, active skin infections, or other conditions that might interfere with study evaluation; immunocompromised patients or patients with a history of malignant disease; patients who had received phototherapy or systemic therapy known or suspected to have an effect on AE; and patients with known hypersensitivity to the study medications. Patients were allowed to apply only the topical medications prescribed. Therapies that were prohibited during the study included ultraviolet (UV) therapies, systemic antihistamines, systemic corticosteroids, systemic immunosuppressive medications, and traditional medications. Patients were permitted paracetamol, oral antibiotics, and intranasal and inhaled corticosteroids as needed if use was restricted to manufacturer-approved indications and doses did not exceed the maximal approved doses. Patients were allowed to withdraw from the study at any point in time.

Trial Design

In this prospective, randomized controlled, investigator-blinded trial conducted over 1 year, patients were randomized to two groups according to a computer-generated blinded randomization list. Group A applied emollient followed by TCS 15 minutes later, and group B applied TCS followed by emollient 15 minutes later.

Enrolled patients were given an emollient (aqueous cream) and two types of TCS (hydrocortisone acetate 1% cream (cortisone cream; Dynapharm, Prai, Pulau Pinang, Malaysia) for facial eczema and clobetasone butyrate 0.05% cream (Eumovate; GlaxoSmithKline, Petaling Jaya, Selangor, Malaysia) for the rest of the body. During the study, the parent or caregiver applied a thin layer of TCS over affected areas (~12 hours apart) soon after bathing, based on fingertip unit measurement.

The emollient (aqueous cream) was applied generously over the patient's whole body twice per day soon after bathing 15 minutes before or after TCS according to the group to which the patient was randomized. The containers containing aqueous cream and TCS were numbered according to the order of application. Parents or caregivers were also told to use aqueous cream as a soap substitute during the study and to ensure that their children took short baths twice per day before application of topical medications. Only parents or main caregivers were allowed to apply the medications provided, to promote better adherence. Parents or caregivers were asked to bring the partially used containers of medicine to each visit to ensure adherence to the dose and sequence of medication. Parents were asked to show which container was used first to determine whether they were adhering to the sequence. They were given a diary to record the application of medicine and any adverse effects that occurred.

Patient assessments were conducted at baseline, week 1, and week 2. At the baseline visit, the investigator confirmed the diagnosis of AE using the Hanifin and Rajka modified diagnostic criteria (4) and severity using the Rajka and Langeland criteria (5). The investigator was trained to use these criteria using the UK Diagnostic Criteria for Atopic Eczema Manual by University of Nottingham and had passed the validity testing (6).

Efficacy Endpoints

The following assessments were made at each visit: percentage of body surface area (BSA) with AE estimated from four designated body regions (head and neck, upper limbs, trunk including groin, lower limbs) and the Physician's Assessment of Individual Signs in each of these regions. The results of these assessments were used to calculate the Eczema Area and Severity Index (EASI) score. Other assessments at each visit included parent or caregiver assessment of itch and adverse events, adherence, and concomitant medication intake.

Outcome Measures

The primary outcome measured was the change in EASI score from baseline to week 2 (end of study) or the last postbaseline assessment in the case of early discontinuation. Secondary outcome measures included the percentage of BSA affected and parent or caregiver assessment of itch. Safety endpoints included overall incidences of all adverse events that the parent or caregiver reported or that the investigator observed.

Ethical Issue

The Ministry of Health Malaysia Research & Ethics Committee approved this study, which was conducted according to Good Clinical Practice. It is registered in the National Medical Research Register (registration no. NMRR-10-602-5917).

Statistical Analysis

Results were analyzed using SPSS version 13 (SPSS, Chicago, IL). Descriptive statistics were used to calculate percentages, means, medians, means, and standard deviations. Statistical analysis was performed using nonparametric tests (Mann–Whitney *U*-test and Friedman analysis of variance). Sample size was estimated based on Cohen (7), because no historical

data were available from studies using clobetasone butyrate. A sample size of 64 per group was required to achieve a medium effect size with 80% power and $p < 0.05$ as significant. Because approximately 20% of patients were expected to withdraw from the study, the total sample size needed was estimated at 154.

RESULTS

The workflow is shown in Fig. 1. A total of 104 patients screened between June 2010 and May 2011 met the inclusion criteria, but only 46 patients who met the exclusion criteria entered the study. Twenty-six patients were randomized to group A and 20 to group B. Eighteen patients withdrew from the study or were lost to follow-up (eight in group A, 10 in group B). The ages of the patients recruited ranged from 4 to 58 months (mean 28.2 ± 15.9 months, median 27.5 months). The sociodemographic characteristics of the subjects are shown in Table 1.

Group A had significant improvement in the EASI score, percentage of BSA affected, and itch score from baseline to weeks 1 and 2. Group B had significant improvement from baseline in the EASI score at week 1 and itch score at week 2, but no change in the percentage of BSA affected. The improvement in the EASI score, percentage of BSA affected, and itch score seemed greater in group A than group B, but it

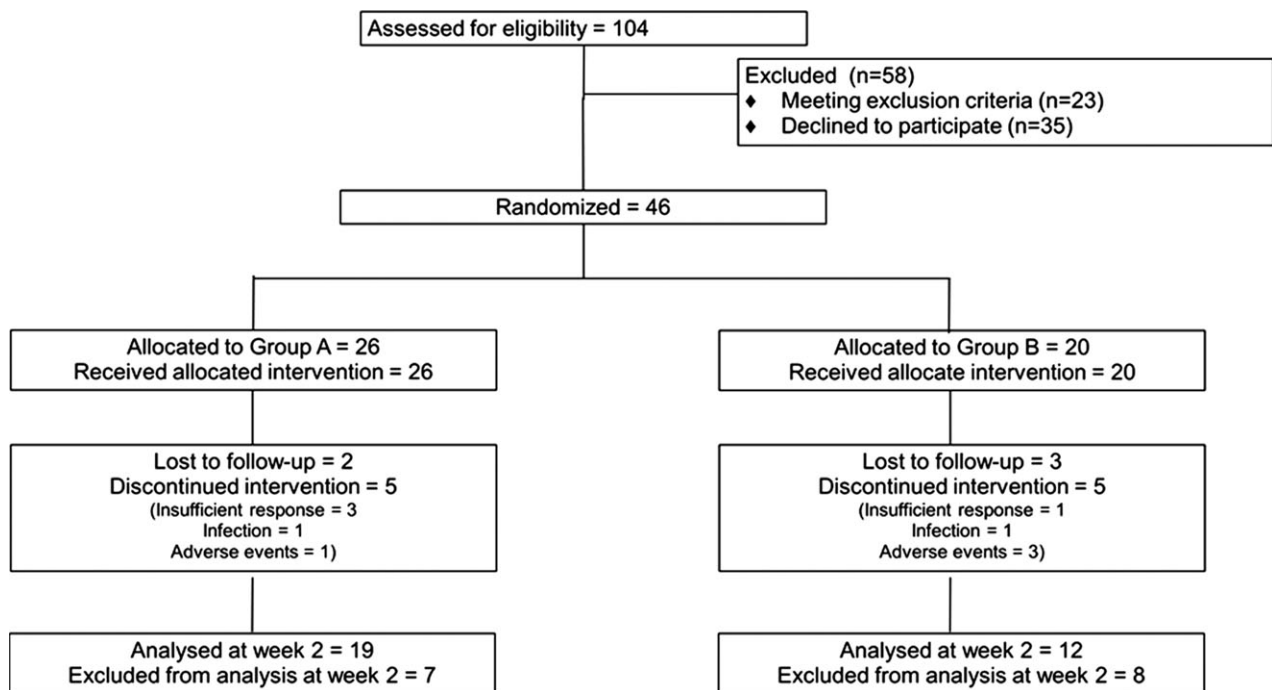


Figure 1. Of 104 patients assessed for eligibility, 58 were excluded because they did not meet the inclusion criteria or declined to participate. During follow-up, 19 participants in group A and 12 in group B completed all return visits.

TABLE 1. Sociodemographic Data of Participants

	Group A, <i>n</i> = 26 (56.5%)	Group B, <i>n</i> = 20 (43.5%)
Sex, <i>n</i> (%)		
Male	13 (50)	14 (70)
Female	13 (50)	6 (30)
Age, months, mean $\pm$ SD, median (range)	26.1 $\pm$ 17.0, 22.5 (4.0–56.0)	31.0 $\pm$ 14.4, 32.0 (6.0–53.0)
Ethnicity, <i>n</i> (%)		
Malay	26 (100)	16 (80)
Chinese	0	0
Indian	0	4 (20)
Overall duration of atopic eczema, months, mean $\pm$ SD, median (range)	19.2 $\pm$ 17.0, 16.5 (2.0–53.0)	23.2 $\pm$ 13.5, 24.0 (4.0–53.0)
Duration of current episode, months, mean $\pm$ SD, median (range)	3.1 $\pm$ 7.6, 0.5 (0.03–36.0)	2.3 $\pm$ 3.0, 1 (0.1–12.0)
Severity of atopic eczema on day 1, <i>n</i> (%)		
Moderate	16 (61.5)	14 (70.0)
Severe	10 (38.5)	6 (30.0)
Adverse effects, <i>n</i> (%)		
Skin burning	0 (0)	4 (20.0)
Pruritus	4 (15.4)	6 (30.0)
Skin erythema	5 (19.2)	7 (35.0)
Rash	3 (11.5)	1 (5.0)
Eye irritation	2 (7.7)	1 (5.0)
Other	3 (11.5)	3 (15.0)

SD, standard deviation.

TABLE 2. Changes in Eczema Area and Severity Index (EASI) Score, Percentage of Body Surface Area (BSA) Affected, and Itch Score

	Baseline, median (IQR)	Week 1, median (IQR)	Week 2, median (IQR)	p-Value*
Disease severity–EASI				
Group A	13.3 (6.8–19.2) (<i>n</i> = 26)	7.7 (3.6–13.5) (<i>n</i> = 24)	4.6 (2.7–11.5) (<i>n</i> = 19)	0.000 [‡]
Group B	15.5 (7.3–22.0) (<i>n</i> = 20)	10.6 (3.3–14.9) (<i>n</i> = 16)	10.4 (4.9–16.1) (<i>n</i> = 12)	0.11 [§]
p-Value [†]	0.36	0.82	0.11	
Percentage of BSA affected				
Group A	27.3 (16.5–40.8) (<i>n</i> = 26)	16.3 (11.9–34.5) (<i>n</i> = 24)	12.0 (8.0–27.0) (<i>n</i> = 19)	0.002 [‡]
Group B	35.3 (20.3–55.5) (<i>n</i> = 20)	24.8 (10.1–48.4) (<i>n</i> = 16)	28.0 (8.0–46.0) (<i>n</i> = 11)	0.69
p-Value [†]	0.30	0.47	0.08	
Itch score				
Group A	6.0 (5.0–8.0) (<i>n</i> = 26)	4.0 (3.0–6.0) (<i>n</i> = 23)	4.0 (3.0–6.0) (<i>n</i> = 19)	0.001 [‡]
Group B	6.0 (5.0–8.0) (<i>n</i> = 20)	6.0 (3.0–8.0) (<i>n</i> = 17)	4.0 (2.5–7.0) (<i>n</i> = 12)	0.007 [¶]
p-Value [†]	0.95	0.42	0.71	

IQR, interquartile range.

*Friedman analysis of variance.

†Mann–Whitney *U*-test.

‡Significant difference from baseline at weeks 1 and 2.

§Significant difference from baseline to week 1.

¶Significant difference from baseline to week 2.

was not statistically significant at every assessment (Table 2).

Safety and Tolerability

Patients in group A experienced 12 adverse events related to study treatment and 15 adverse events occurred in group B. Only one patient in group A and three in group B withdrew because of adverse events. No patients experienced serious adverse events in either treatment group. The most com-

mon adverse events were pruritus and erythema (Table 1).

DISCUSSION

The management of AE, which includes avoidance of triggers, controlling exacerbating factors, skin hydration with moisturizers, and topical antiinflammatory medications, is challenging. The cornerstone of management is moisturizing the skin and using TCS to control inflammation (8).

There are no published guidelines on the best order of application of emollient and TCS in children with AE. The recommendations are conflicting and not evidence based. The Guideline Development Group (GDG) of NICE believes that emollients are the most important treatment for AE because they restore the defective skin barrier (3), but the GDG states that the preferred order of application of emollient and TCS is not known. It is recommended that there should be a short interval (several minutes) between application of TCS and an emollient where practicable (3). National Health Service Clinical Knowledge Summaries recommend that when both treatments are being used, the emollient should be used first, followed by the TCS, preferably after several minutes' wait (9). Similarly, the International Skin Care Nursing Group, in their Best Practice in Emollient Therapy guideline, states that moisturizers should be allowed to absorb into the skin before the application of a therapeutic product (10).

Some experts recommend that emollients be applied after the TCS. A MeReC bulletin, published by the National Prescribing Centre, states that if a TCS is being used, emollient should be applied after the TCS (11). Smoker et al (12) suggested that if occlusive emollients are applied before the TCS, penetration of the TCS may be prevented. Likewise, if an emollient is applied after a TCS, there is the potential for diluting or smearing. Smoker et al were unable to find any conclusive evidence to support either stance (12). Wasserbauer and Ballow (13), in an article published in the *American Journal of Medicine*, recommend that the TCS should be applied before emollients once or twice daily during a flare.

As a result of these conflicting recommendations, health care professionals advise patients differently, leading to inconsistent advice that may lead to confusion in patients and thus affecting adherence. This study was conducted with the objective of answering the question of which topical cream to apply first, which NICE has made a research priority.

Our study shows that application of TCS plus emollient provides an effective treatment regimen to control AE, as evidenced by the statistically significant improvements in the EASI score, percentage of BSA affected, and itch score from baseline to weeks 1 and 2 in group A and statistically significant improvement in the EASI score at week 1 and itch score at week 2 in group B. The order of application of emollient (aqueous cream) and TCS does not make a difference in the treatment of AE in children, as improvement in the EASI score, percentage of BSA

affected, and itch score were not statistically significantly different between groups A and B.

The limitations of our study are as follows: small sample size, parents or caregivers apply the topical medications at home without supervision, and high dropout rate and difficult recruitment because patients were not given any financial assistance to cover their transportation costs. Despite these limitations, it can be viewed as a pilot study and as an impetus to stimulate further research into this controversial topic. Further larger studies are needed to clarify this issue so that health care professionals can give standardized advice to improve control of eczema and reduce confusion in caregivers and patients.

REFERENCES

1. Ring J, Alomar A, Bieber T et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012;26:1045–1060.
2. Grimalt R, Menheaud V, Cambazard F. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis. *Dermatology* 2007;214:61–67.
3. National Institute for Health and Clinical Excellence. Atopic eczema in under12s: diagnosis and management. December 2007 [online]. <http://www.nice.org.uk/Guidance/CG57> (accessed on December 10, 2010).
4. Williams HC, Burney PG, Hay RJ et al. The UK working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383–396.
5. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol* 1989;144:13–14.
6. Williams HC. So How Do I Define Atopic Eczema? A Practical Manual for Researchers Wishing to Define Atopic Eczema [online]. <http://www.nottingham.ac.uk/dermatology/eczema/index.html> (accessed on February 3, 2011).
7. Cohen J. A Power Primer. *Psychol Bull* 1992;112:155–159.
8. Eichenfield LF, Tom WL, Berger TG et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116–132.
9. CKS Eczema—Atopic—Management. Clinical Knowledge Summaries 2008 [online]. http://www.cks.library.nhs.uk/eczema_atopic (accessed on December 10, 2010).
10. Ersser S, Maguire S, Nicol N et al. A best practice statement for emollient therapy. *Dermatol Nursing* 2007;1:1–19.
11. National Prescribing Centre. The use of emollients in dry skin. *MeReC Bulletin* 1998;9:47.
12. Smoker A. Topical steroid or emollient – which one do you apply first? An investigation into the sequencing of topical steroid and emollient application and the most clinically effective method of application. Unpublished report, University of Southampton, 2007.
13. Wasserbauer N, Ballow M. Atopic dermatitis. *Am J Med* 2009;122:121–125.