European Review for Medical and Pharmacological Sciences 2012; 16: 1989-1993

Hydrocortisone acetate alone or combined with mupirocin for atopic dermatitis in infants under two years of age – a randomized double blind pilot trial

F. CANPOLAT, M. ERKOÇOĞLU*, H. TEZER**, C.N. KOCABAŞ*, B. KANDI

Clinic of Dermatology, Ministry of Health, Yildirim Beyazit Education and Research Hospital, Ankara, Turkey
*Department of Pediatric Allergy, and **Department of Pediatric Infectious Diseases, Ministry of Health, Ankara Childrens Hematology and Oncology Hospital, Ankara, Turkey

Abstract. – BACKGROUND: The skin of patients with atopic dermatitis (AD) is heavily colonized with *Staphylococcus (S.) aureus*, even at uninvolved sites. Toxins secreted by the majority of *S. aureus* on the skin behave as superantigens and can directly influence the disease activity, although clinical signs of bacterial superinfection might be absent.

OBJECTIVES: This study was conducted to compare the efficacy of hydrocortisone cream, combined with mupirocin or alone with emmolient ointment for the treatment of mild to moderate AD in infants between six months and two years of age.

MATERIALS AND METHODS: A total of 26 patients with mild to moderate AD were randomized to receive hydrocortisone, hydrocortisone+ mupirocin or emmolient ointment twice daily in one week and followed-up for 8 weeks in a blind study. Efficacy evaluation made by SCORAD and eczema area and severity index (EASI) at baseline, day 7, and weeks 2, 4, and 8. Possible adverse events were recorded to evaluate safety.

RESULTS: At the end of study, 65% (17 of 26) of the patients were treated successfully with hydrocortisone ointment based on SCORAD and EASI scores. Also there was a significant improvement in patients combined with mupirocin ointment [74% (20 of 27)]. The percent improvement from baseline in EASI scores was also significantly greater in hydrocortisone and combined group compared with emmolient-treated patients (36%) ($p = 0.0187$, $p = 0.012$ respectively).

CONCLUSIONS: Monotherapy with hydrocortisone ointment is the main treatment in infants with mild to moderate AD and combination with mupirocin is safe and effective often needed because of possible *Staphylococcus* carriage.

Key Words:
Atopic dermatitis, Infants, Hydrocortisone ointment, Mupirocin, *Staphylococcus*.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with intense pruritus as its hallmark symptom, and often follows a chronic, relapsing course[1] and has a negative impact on the quality of life of children and their parents that affects a large number of children and adults in industrialized countries. The one-year prevalence in 11-year-old children with AD, as studied in the Global International Study of Asthma and Allergies in Childhood trial, ranged from 1% to 20%, with the highest prevalence typically found in Northern Europe[1]. In 45% of children, the onset of AD occurs during the first 6 months of life, during the first year of life in 60%, and before the age of 5 years in at least 85% of affected individuals[2]. In those children with onset before the age of 2 years, 20% will have persisting manifestations of the disease, and an additional 17% will have intermittent symptoms by the age of 7 years[1,2].

Topical glucocorticosteroids are still an important choice for the treatment of acute exacerbations in AD[3,4]. Aside from an anti-inflammatory effect, treatment with topical steroids contributes to a reduction of skin colonization with *S. aureus* and, therefore, might affect a further trigger factor of AD[5,6]. The skin of patients with AD is heavily colonized with *S. aureus*, even at uninvolved sites and toxins secreted by the majority of *S. aureus* on the skin behave as superantigens and can directly influence the disease activity, although clinical signs of bacterial superinfection might be absent[7,8]. Most patients with AD are colonized with *S. aureus* and experience exacerbation of their skin disease after infection with this organism[9]. In

Corresponding Author: Filiz Canpolat, MD; e-mail: filizcanpolat@hotmail.com

patients with AD with bacterial infection, treatment with antistaphylococcal antibiotics can result in reduction of skin disease[1]. However, to the best of our knowledge there is not any previous study which evaluates the efficacy of topical steroids alone or combination with antimicrobial agents and compares to non-pharmacologic agents in infants with AD under two years of age. So that this study planned to compare the effect of hydrocortisone cream, combined with mupirocin or alone with emmolient ointment for the treatment of mild to moderate AD in infants between six months and two years of age.

Materials and Methods

This pilot study was a blind, 8 week trial that involved 83 infants with a diagnosis of AD based on the Hanifin and Rajka criteria[10] and with an evaluation of severity based on Rajka and Langeland criteria[11]. Parents gave informed consent and local institutional Ethical Board approved this protocol. The parents who did not want to use pharmacological agents informed and than consisted the control (only emmolient) group. Caregivers, investigators, and clinical staff were blinded to treatment except parents. Drugs prescribed by a different investigator and clinical follow-up dermatologic assessment made by a different clinican. Infants between six months and 2 years of age with a diagnosis of mild to moderate AD involving 2% to 30% of the body were enrolled in the study. Before all medications swab cultures obtained from lesions for *S. aureus* colonization. A thin coating of either hydrocortisone or mupirocin or both ointment was applied twice daily to areas affected with AD at least 2 hours before bathing for up to seven days by parents. The hydrocortisone+mupirocin group used hydrocortisone at morning and evening and mupirocin at noon and at night at least 2 hours before bathing. Nonsteroidal immunosuppressants (pimecrolimus), other investigational drugs, systemic corticosteroids, ultraviolet light therapy, as well as concomitant topical medications (including other topical corticosteroids, topical H1 and H2 antihistamines, and other topical antimicrobials) were not allowed during the treatment period. Use of sunscreen was allowed, and application of nonmedicated emollients was permitted on nontreatment areas. Use of cosmetics on treatment sites was prohibited. Oral antihistamines and antibiotics were not allowed or excluded from the study.

The main outcome measure was SCORAD (Severity Scoring of Atopic Dermatitis index) and eczema area and severity index (EASI) scores, percentage of total body surface area (%BSA) affected. The SCORAD index includes the assessment, by a physician, of objective signs (extent and intensity) and of subjective symptoms (pruritus and sleep disturbance) compiled on an analogue scale by the parents. Extent was calculated using the "rule of nine" and expressed the skin surface area involved. Items that were evaluated in the intensity criteria were erythema, oedema/papulation, oozing/crusts, excoriations, lichenification, and dryness of involved skin (from 0 to 3 points for each item). The final score was then calculated using the following equation: A/5 + 7B/2 + C (A = extent; B = intensity; C = subjective symptoms). The SCORAD index ranges lies between 0 and 103. Based on the SCORAD index results, AD has been classified, as reported, into mild (< 25), moderate (25-50) and severe (> 50) forms[12].

The EASI is also a composite index, including the assessment of disease extent and percent of involved body surface area, converted to a proportional factor (scale from 0 to 6, in four body regions (head and neck, lower limbs, upper limbs, and trunk). The proportion allocated to each body region depends on the patient's age. In patients aged less than 7 years, proportions are 20 % for head and neck, 20 % for upper extremities, 30 % for trunk and 30 % for lower extremities. The EASI also includes an assessment of erythema (E), infiltration and_or papulation (I), excoriation (Ex) and lichenification (L), each on a scale from 0 to 3. The EASI's minimum score is 0 and the maximum is 72. The algorithm for calculating the EASI uses, for each body region, the sum of the clinical sign scores (E + I + Ex + L) multiplied by the body surface area, multiplied by the proportional factor. The total EASI score is the sum of the four body-region scores[13].

"Treatment success" was defined as a > 50% recovery of the lesions or > 50% decrease of EASI or SCORAD indexes.

Statistical Analysis

Sample size was based on the binomial distribution with the objective to detect a difference in success rate between the control and the treatment groups with 95% power and a 2-sided .05 significance level. Based on estimated success rates of 50% for hydrocortisone or combined group and 30% for emmolient group, 25-30 pa-

tients would be required for each treatment group[14]. Kruskal-Wallis and Mann-Whitney tests used for comparing SCORAD and EASI indexes between groups.

Results

After exclusions 83 infants were enrolled the study. Thirty of 83 were consisted group 1 (control, only emollient), 26 were designed for group 2 (Steroid treated) and 27 were served as combined group (group 3, steroid plus mupirocin treated). Median age of infants was 14 months (6-24 months range). SCORAD and EASI indexes were similar for all groups at the begining of the study (day 0). There was no difference between groups for bacterial colonization. After the treatment (day 8) both severity indexes were compared for all groups and there were statistically significant differences between control and treatment groups, additionaly there was also difference between steroid and combined group for EASI ($p = 0.02$).

At the end of study (day 60), 65% (17 of 26) of the patients were treated successfully with hydrocortisone ointment based on SCORAD and EASI scores. Also there was a significant improvement in patients combined with mupirocin ointment [74% (20 of 27)]. The percent improvement from baseline in EASI scores was also significantly greater in hydrocortisone and combined group compared with emollient-treated patients (36%) ($p = 0.0187$, $p = 0.0$ respectively). These data are summarized in Table I and scores are compared in Figures 1 and 2.

Discussion

Secondary bacterial skin infections and treatment failure in AD are linked to the high rates of *S. aureus* colonization in the AD population (76%-100%, compared with 2%-25% for healthy control subjects)[15]. To the best of our knowledge there is no previous study which compares topical steroids combined with topical antibacterials in infants with AD under two years of age. Therefore, we observed that combination of these two topical treatment seems to be better than steroid alone in infants with AD.

Harmful effects of *S. aureus* have led clinicians to consider treatment of bacterial growth as an important recovery for AD. Although some reports suggested that topical antibiotic application to all affected areas could improve clinical severity, more recent studies did not show an effect[16-17]. Concomitant application of topical mupirocin and corticosteroid preparations to lesional skin for 28 days did not decrease the clinical severity of AD more significantly than did topical corticosteroid administration alone[18]. Similarly, adjunctive use of topical fusidic acid treatment for 8 weeks did not show improvement in AD than did the use of fluticasone propionate ointment or tacrolimus ointment alone[19]. Gentian violet decreases *S. aureus* density and improves AD severity[20], but is not cosmetically acceptable especially in infants. In addition, use of chlorhexidine has been found to cause irritant contact dermatitis[21]. Skin exposure to silver-impregnated textiles and treatment with potent topical steroid preparations, calcineurin inhibitors, or phototherapy also have reduced the burden of *S. aureus* on atopic skin, which may contribute to therapeutic potential[22-26]. In pediatric population, use of dilute bleach

Table I. Comparison of study groups.

	Group 1, control, (only emollient) n = 30	Group 2, (steroid) n = 26	Group 3, (combined) n = 27	*p*
Age, months (range)	15 (6-24)	13.6 (6-24)	13.3 (6-24)	ns
Staphylococcus positivity, n (%)	12 (36%)	10 (38%)	11 (40%)	ns
EASI on day 0	5.8 (2-8)	5.8 (2-9)	5.9 (3-8)	ns
EASI on day 8	5.5 (2-8)	5.1 (2-7)	4.2 (2-6)	* ¥
SCORAD on day 0	32 (24-38)	31 (22-39)	30 (23-37)	ns
SCORAD on day 8	30 (23-34)	27 (20-33)	26 (21-32)	#
Treatment success, %	36	65	74	

* $p = 0.02$ control vs steroid groups, $p = 0.001$ control vs combined group, # $p = 0.014$ control vs steroid groups $p = 0.006$ control vs combined group. ¥ $p = 0.031$ for EASI on day 8 between Group 2 and 3.

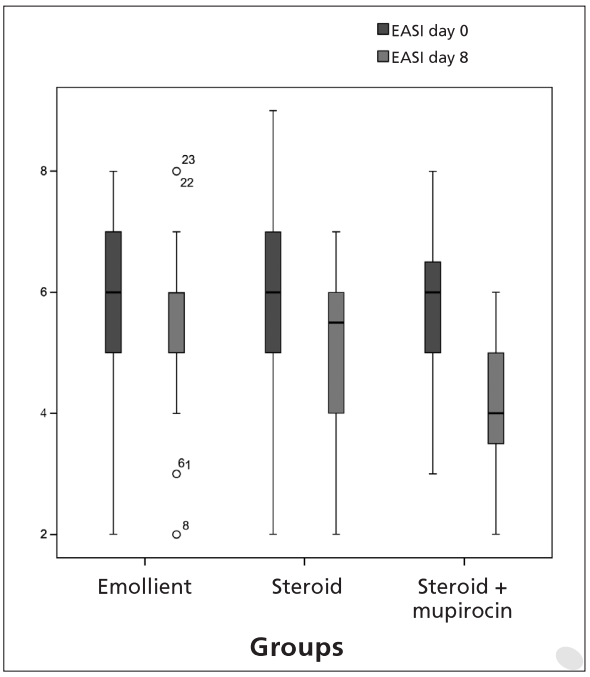

Figure 1. Comparison of EASI scores of groups before (on day 0) and after the reatment (day 8).

baths with intermittent intranasal application of mupirocin ointment decreased the clinical severity of atopic dermatitis in patients with clinical signs of secondary bacterial infections[27].

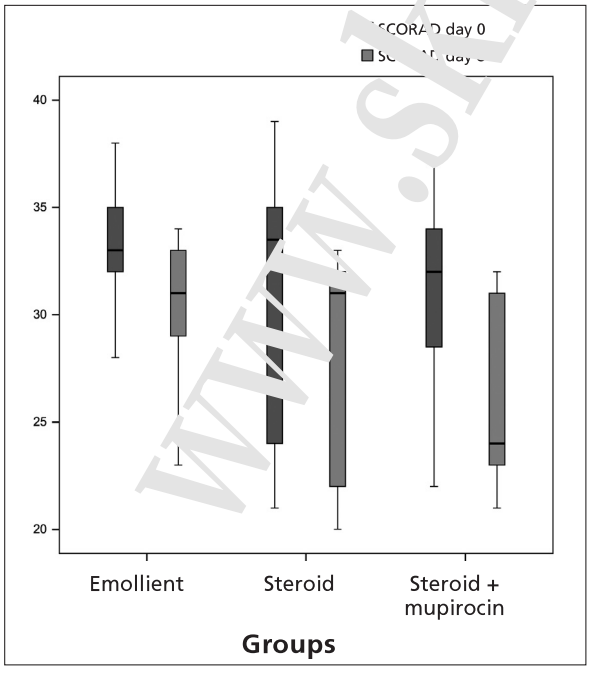

Figure 2. Comparison of SCORAD indexes of groups before (on day 0) and after the treatment (day 8).

We concluded that, topical steroids are the main treatment of AD but combination with mupirocin for *S. aureus* in infants under two years of age with AD seems safe and effective.

References

1) Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, Hamid Q, Kapp A, Leung DY, Lipozencic J, Luger TA, Muraro A, Novak N, Platts-Mills TA, Rosenwasser L, Scheynius A, Simons FE, Spergel J, Turjanmaa K, Wahn U, Weidinger S, Werfel T, Zuberbier T; European Academy of Allergology, Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Group. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy 2006; 61: 969-987.

2) Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U; Multicenter Allergy Study Group. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004; 113: 925-931.

3) Darsow U, Lubbe J, Taieb A, Seidenari S, Wollenberg A, Calza AM, Giusti F, Ring J; European Task Force on Atopic Dermatitis. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2005; 19: 286-295.

4) Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, Schachner LA, Sidbury R, Whitmore SE, Sieck CK, Van Voorhees AS. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines. J Am Acad Dermatol 2004; 50: 391-404.

5) Stalder JF, Fleury M, Sourisse M, Rostin M, Pheline F, Litoux P. Local steroid therapy and bacterial skin flora in atopic dermatitis. Br J Dermatol 1994; 131: 536-540.

6) Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and Staphylococcus aureus in atopic dermatitis. J Am Acad Dermatol 1992; 27: 29-34.

7) Breuer K, Kapp A, Werfel T. Bacterial infections and atopic dermatitis. Allergy 2001; 56: 1034-1041.

8) Breuer K, HAussler S, Kapp A, Werfel T. Staphylococcus aureus: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. Br J Dermatol 2002; 147: 55-61.

9) Leung DY. Infection in atopic dermatitis. Curr Opin Pediatr 2003; 15: 399-404.

10) Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl 1980; 92: 44-47.

11) Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl 1989; 144: 13-14.

12) Pucci N, Lombardi E, Novembre E, Farina S, Bernardini R, Rossi ME, Favilli T, Vierucci A. Urinary eosinophil protein X and serum eosinophil cationic protein in infants and young children with atopic dermatitis: correlation with disease activity. J Allergy Clin Immunol 2000; 105: 353-357.

13) Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001; 10: 11-18.

14) http://www.dssresearch.com/toolkit/spcalc/power_a2.asp

15) Higaki S, Morohasi M, Yamagishi T, Hasegawa Y. Comparative study of staphylococci from the skin of atopic dermatitis patients and from healthy subjects. Int J Dermatol 1999; 38: 265-269.

16) Lever R, Hadley K, Downey D, Mackie R. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. Br J Dermatol 1988; 119: 189-198.

17) Ravenscroft JC, Layton AM, Eady EA, Murtagh M, Coates P, Walker M, Cove JH. Short-term effects of topical fusidic acid or mupirocin on the prevalence of fusidic acid resistant (FusR) Staphylococcus aureus in atopic eczema. Br J Dermatol 2003; 148: 1010-1017.

18) Gong JQ, Lin L, Lin T, Hao F, Zeng FQ, Bi ZG, Li D, Zhao B. Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. Br J Dermatol 2006; 155: 680-687.

19) Hung SH, Lin YT, Chu CY, Lee CC, Ling TC, Yang YH, Wang LC, Chiang BL. Staphylococcus colonization in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. Ann Allergy Asthma Immunol 2007; 98: 51-56.

20) Brockow K, Grabenhorst P, Abeck D, Traupe B, Ring J, Hoppe U, Wolf F. Effect of gentian violet, corticosteroid and tar preparations in *Staphylococcus aureus*-colonized atopic eczema. Dermatology 1999; 199: 231-2[illegible]

21) Wendt C, Schinke S, Württemberger M, Oberdorfer K, Bock-Hensley O, von Baum H. Value of whole-body washing with chlorhexidine for the eradication of methicillin-resistant *Staphylococcus aureus*: a randomized, placebo-controlled, double-blind clinical trial. Infect Control Hosp Epidemiol 2007; 28: 1036-1043.

22) Nilsson EL, Hjenning CG, Magnusson J. Topical corticosteroids and *Staphylococcus aureus* in atopic dermatitis. J Am Acad Dermatol 1992; 27: 29-34.

23) Saldeen T, Fleury M, Sourisse M, Rostin M, Pheline E, Lindh P. Local steroid therapy and bacterial skin flora in atopic dermatitis. Br J Dermatol 1994; 131: 536-540.

24) Pournaras CC, Lubbe J, Saurat JH. Staphylococcal colonization in atopic dermatitis treatment with topical tacrolimus (FK506). J Invest Dermatol 2001; 116: 480-481.

25) Gauger A, Mempel M, Schekatz A, Shafer T, Ring J, Abeck D. Silver-coated textiles reduce *Staphylococcus aureus* colonization in patients with atopic eczema. Dermatology 2003; 207: 15-21.

26) Yoshimura-Mishima M, Akamatsu H, Namura S, Horio T. Suppressive effect of ultraviolet (UVB and PUVA) radiation on superantigen production by *Staphylococcus aureus*. J Dermatol Sci 1999; 19: 31-36.

27) Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. Pediatrics 2009; 123: e808-e814.