The Good Skin Care Practices and Emollient Use since Early Infancy as the Primary Prevention of Infantile Atopic Dermatitis among Infants at Risk: a Randomized Controlled Trial

Pajaree Thitthiwong, M.D.,* Thantida Koopitakkajorn, M.D.**

**Division of Pediatric Dermatology, **Department of Pediatrics, Phramongkutklao Hospital, Phramongkutklao College of Medicine, Bangkok, Thailand.*

ABSTRACT

Objective: The study aimed to determine whether enhancing the skin barrier since early infancy could reduce the incidence of infantile atopic dermatitis among high risk infants.

Methods: We conducted a prospective, randomized, controlled trial at the Pediatric Clinic, Phramongkutklao Hospital in Bangkok. Eligible infants aged less than 10 weeks with family history of atopy were enrolled and randomly allocated to one of the two groups. The intervention group applied emollient at least once daily all over the body together with receiving good skin care practice advice, whereas the control group received only good skin care practice advice. All infants were followed up and assessed at 2, 4, 6 and 9 months old.

Results: Fifty-two infants were enrolled, 25 in the intervention group and 27 in the control group. At 9 months old follow-up, none in the intervention group had infantile atopic dermatitis, whereas 14.8% in the control group developed infantile atopic dermatitis (p-value < 0.05). The mean age at diagnosis of infantile atopic dermatitis was 5.5 months.

Conclusion: Regular emollient application together with good skin care practice since early infancy could reduce the incidence of infantile atopic dermatitis among high risk infants.

Keywords: Infantile atopic dermatitis; primary prevention; emollient (Siriraj Med J 2020; 72: 41-46)

INTRODUCTION

Infantile atopic dermatitis (IAD) is chronic inflammatory dermatosis with increasing prevalence worldwide. In 2009, the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three provided comprehensive data on the prevalence of atopic dermatitis stressing the global concern of the increasing trends both in developing and developed countries.[1] This study proposed the prevalence of atopic dermatitis in the age group 6 to 7 years ranging from 0.9% to 22.5% and 0.2% to 24.6% for the group of 13 to 14 years old. Interestingly, the high prevalence of 15% or more in the age group 6 to 7 years has been found in many countries across the globe including the Asia-Pacific region. One study conducted in Bangkok reported the prevalence of atopic dermatitis at 9.4% in the older age group.[2]

To our knowledge, factors responsible for developing of IAD are multifactorial including genetic, environment, immune dysregulation and dysfunctional skin barrier.[3] For the genetic aspect, when one or both of parents are

Corresponding author: Pajaree Thitthiwong
E-mail: pajareepmk@gmail.com
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ORCID ID: http://orcid.org/0000-0003-4236-450X
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diagnosed with any allergic disease, their children could have a 40 to 50% chance to develop atopic dermatitis. Infants who develop IAD before 2 years of age with persisting disease would have the risk to develop other atopic diseases as a part of the atopic march.[4-5] The chronic relapsing itchy eczematous skin with typical locations for particular age is known to be the hallmarks of atopic dermatitis, affecting the quality of life not only of the patients but also their family members.[6-7]

Various modalities for the primary prevention of IAD have been studied, for example, exclusive breastfeeding, hydrolyzed protein formula, maternal antigen avoidance, prebiotics and probiotics but without promising evidence.[8-13] The skin barrier dysfunction and immune dysregulation are known as the key pathogenesis of IAD.[14-15] Hence, the hypothesis of enhancing the skin barrier since birth or early infancy to impede penetration of allergens and consequently prevent inflammatory cytokines release may play an important role to prevent the disease. Simpson et al. investigated the effect of emollient on the infant skin barrier for the primary prevention of IAD among high risk infants with positive outcomes.[16-17] Horimukai et al. also studied the primary prevention of IAD among high risk infants in Japan and reported reduced IAD incidence among infants regularly using emollient.[18]

We conducted a study to determine whether good skin care practice together with regular emollient use since early infancy could reduce the incidence of IAD among high risk infants.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department in Bangkok (IRB RTA; Ro51h/58). A prospective, randomized, controlled trial among healthy high risk infants for whom at least one of their parents or siblings presented any allergic diseases was conducted at the Pediatric Outpatient Department of Phramongkutklao Hospital in Bangkok from 2016 to 2017. Funding was granted by Phramongkutklao Hospital, and investigators declared they had no conflict of interest. Thailand's clinical trial registration (TCTR20161208001).

Study population

Eligible infants were defined as healthy, term infants, aged less than 10 weeks old whose parent(s) or sibling(s) had a history of any allergic disease such as atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, food allergy or other allergic conditions.

Infants known to have major congenital anomalies, immunodeficiency syndrome, any skin disease other than infantile seborrheic dermatitis or neonatal acne were excluded from the study. Infants whose parents reported regular emollient use before enrollment were also excluded. Written informed consent forms were obtained from all enrolled families.

Study design and intervention

The enrolled infants were allocated to either the control or intervention group by block of 4 randomization with allocation concealment using opaque envelopes. Infants in the intervention group were assigned to regularly apply the hospital formulated emollient containing white petrolatum, stearyl alcohol, propylene glycol and glycerin, named "Cold Cream" all over the body except periorbital and perioral areas at least once daily shortly within 3 to 5 minutes after bathing and padding dry the baby skin. However, those parents or caregivers of infants in the control group were asked not to apply any skin care products on the baby skin except using the gentle liquid baby cleansers during bathing and the barrier ointment or cream on diaper areas as needed. Caregivers in both groups were given verbal advice for good skin care practice repeatedly during every visit. The good skin care practice comprised the proper duration of bathing of 5 to 10 minutes with tap or lukewarm water, bathing not more than twice daily and using only a minimal amount of gentle liquid baby cleansers of any manufactures. Bath oil, bubble bath or any bath additives were not allowed to be used in both groups.

Appointments with investigators were set up during their regular well baby clinic visits at 2, 4, 6 and 9 months old at the Pediatric Outpatient Clinic. One unblinded investigator would perform a general physical examination, growth and developmental milestone evaluation, general health supervision, routine vaccination and advice regarding good skin care practice to every caregiver of the infants in both groups. The intervention group infants aged less than 6 months received Cold Cream, 180 grams and the infants aged 6 months or older received 240 grams of Cold Cream per visit. The parents in the intervention group were asked to bring back the empty bottles of Cold Cream to confirm their compliance. During each visit, the infants in both groups would be sent to another room and receive only the skin examination and evaluation for the diagnosis of infantile atopic dermatitis by a pediatric dermatologist who was blinded as to group allocation. Neither blood test nor equipment used for transepidermal water loss or stratum corneum hydration measurements were used in this study.

Outcomes

The primary outcome was the cumulative incidence of IAD in both groups. The diagnostic criteria for atopic dermatitis was based on the atopic dermatitis guidelines by Eichenfield et al. in 2014.[6] The secondary outcomes were mean age of onset of IAD, adverse reaction of Cold Cream application and the factors associated with developing IAD. The study end points were defined when the enrolled infants developed IAD or when the infants were 9 months old.

Statistical analysis

The sample size needed to compare two proportions was calculated between groups with an expected 60% reduction in IAD incidence based on related studies using $\alpha = 0.05$ and $\beta = 0.20$.[17-18] A sample size of 70 infants (35 in each group) was required.

Statistical analysis was performed by comparing between the two groups by two-sample test proportion. Descriptive data were presented as means (with standard deviation), medians (with inter-quartile range), and percentages.

RESULTS

This study was conducted from January 2016 to April 2017. Initially, 70 eligible families were informed to recruit in this study. Of these, 17 families were unwilling to participate. One of investigators had to move to work in another hospital, then due to time limitation, the enrollment had to stop before reaching the calculated sample size of 70 infants. Then 53 infants were enrolled and randomly allocated to one of the two groups. In all, 26 infants were placed in the intervention group and 27 in the control group. One infant in the intervention group had to leave the study before 9 months old because the family had to move outside Bangkok. A diagram of the participants is shown in Fig 1. The baseline demographic data between groups were comparable (Table 1).

Regarding the primary and secondary outcomes, none of the infants in the intervention group received a diagnosis of IAD which was repeatedly evaluated during each visit up to 9 months old, whereas 4 (14.8%) infants in the control group developed IAD ($p = 0.045$; Table 2). The mean age of the 4 infants at the onset of IAD was 5.5 ± 0.55 months. The dryness of skin or xerosis, assessed by skin examination during the last follow-up visits, was comparable between groups ($p = 0.120$; Table 2). However, the skin dryness was evaluated clinically without transepidermal water loss or skin moisture measurements. None of the 4 IAD infants developed cow's milk protein allergy or any other food allergy.

The exact volume of the Cold Cream used in each infant in the intervention group was not recorded in this study. Most of the parents carried only the empty bottles of Cold Cream to present to the investigator to confirm their compliance. However, the average Cold Cream used monthly for infants less than 6 months was 90 gm and 120 gm for infants 6 months or older. No interventions related to adverse events were reported by the caregivers.

We also studied those factors assumed to have effects on developing IAD including area of residence (suburb or intown residence), feeding type (exclusive or nonexclusive breast feeding), inhouse pets (dogs or cats) and inhouse smoking and found no significant difference between the IAD and non IAD groups (Table 3). The environmental data around the time of the study in Bangkok are presented. The average temperature in Bangkok was 31°C with 66% relative humidity. The mean level of $PM_{2.5}$ (fine particulate matter) was 58.69 $\mu g/m^3$ at the open roadside areas.[19]

DISCUSSION

This comprised a randomized controlled trial conducting to demonstrate a modality for the primary prevention of infantile atopic dermatitis among high risk infants by enhancing the skin barrier with regular use of emollient and educating concerning good skin care practice to caregivers. We found that using Cold Cream or a petrolatum containing moisturizer at least once daily to the whole body of the high risk infants showed a decrease in the cumulative incidence of infantile atopic dermatitis compared with the infants in the control group receiving only the good skin care advice. We designed to enroll only term, healthy high risk infants, because manipulating the preterm or sick infant skin might increase rates of infection. Our results were in the same direction as in the related data from the studies of Simpson EL in the US and Horimukai K in Japan, although our study did not show a strongly significant difference.[17-18] This might have been a result of the small sample size in this study. The related studies demonstrated that daily emollient use among high risk infants significantly decreased the incidence of infantile atopic dermatitis.

Which emollients would be the best to use in this setting? For example, in the hot and humid geographic regions, we would not recommend using pure petrolatum to the infant skin especially during the summer months. Heat rash would be one concern. Instead we would recommend using the oil-in-water emulsions for the normal skin type and the water-in-oil emulsions such as the "Cold Cream" for the dry skin type. In this study,

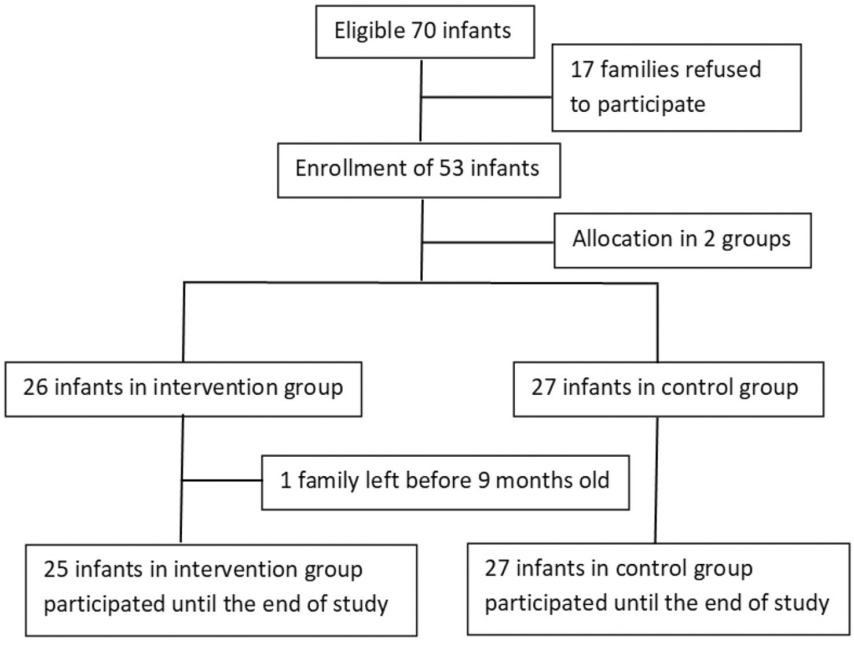

Fig 1. Study population diagram.

TABLE 1. Demographic characteristics.

Characteristics	Intervention (*n* = 25)	Control (*n* = 27)
Sex, n (%)		
Male	12 (48)	13 (48)
Female	13 (52)	14 (52)
Birthweight (g)*	2,270 ± 0.4	2,480 ± 0.7
Age at enrollment (weeks)*	4.19 ± 2.9	4.00 ± 2.9
Both parental atopy (%)	42.3	18.5
Skin at enrollment ** (%)		
Moderate to marked skin dryness	20.0	7.4
Feeding (%)		
Exclusive breast feeding	56.0	80.5
Non-exclusive breast feeding	44.0	19.5
Bathing frequency (%)		
Once daily	48.0	66.7
More than once daily	52.0	33.3
Bathing time (%)		
Up to 10 minutes	92.0	96.3
More than 10 minutes	8.0	3.7
In house pets (%)		
Pets	32.0	37.0
No pets	68.0	63.0
In house smoking (%)		
Smoking	68.0	63.0
No smoking	32.0	37.0
Area of residences (%)		
Urban areas	72.0	48.1
Suburb areas	28.0	51.9

*Data presented as mean ± standard deviation. ** By dermatologic examination.

TABLE 2. Cumulative incidence of IAD and moderate to marked skin dryness (xerosis).

Outcomes	Intervention (*n* = 25)	Control (*n* = 27)	P-value*
Infantile atopic dermatitis	0 (0%)	4 (14.8%)	0.045
Xerosis**	3 (12.0%)	8 (29.6%)	0.120

*Two-sample test of proportion, $p < 0.05$ = statistical significant.
**Evaluated by Pediatric dermatologist at the end of study.
Abbreviation: IAD = infantile atopic dermatitis

TABLE 3. The environmental or biological factors and IAD developing group.

Factors	*n in group* (N = 52)	IAD *n (%)*	P-value*
In town residential areas	31	2 (6.5)	0.683
Exclusive breast feeding	36	3 (8.3)	0.791
In house pets (cats or dogs)	14	3 (21.4)	0.162
In house smoking	34	4 (11.8)	0.130

*Multivariate analysis
Abbreviation: IAD = infantile atopic dermatitis

we did not measure neither the stratum corneum hydration nor the transepidermal water loss (TEWL). Thus, we cannot conclude using scientific data to explain the positive results in the emollient group. These were our limitations.

Scientists have unveiled many associated genes linked to atopic dermatitis such as the Filaggrin gene (*FLG*) for skin barrier dysfunction, β-defensin 1 (*DEFB1*) for the susceptibility to infections, nucleotide-binding oligomerization domain 1 (*NOD1*) and Toll-like receptor 2 (*TLR2*) genes for immune dysregulation.[15] These provide evidence stressing the importance of genetic background for developing atopic dermatitis. In this study, we enrolled high risk infants with any atopic problems among the families, even though the infants from atopic dermatitis families would have higher risk to develop IAD than infants from families with asthma or allergic rhinitis.[20] We realized that some parents could not recall having atopic dermatitis as a part of their atopic march during their childhood.

Allergic sensitization can occur through an impaired skin barrier leading to inflammatory responses and consequently developing atopic rashes. To close the critical gateways for microbes and allergens is to strengthen or to enhance the skin barrier. These strategies of enhancing the skin barrier as early as possible might constitute a convenient and effective method to implement to high risk infants to prevent infantile atopic dermatitis.

According to the ISAAC Phase Three survey, the number of patients with IAD still dramatically and continuously increases over time with higher prevalence (>15%) in many parts of big cities around the world including Asia-Pacific.[1] Because of the small sample size in this study, we could not confirm any correlation between environmental or biological factors such as feeding type, area of residence, smoking or inhouse pets and IAD incidence.

Atopic dermatitis is a public health problem for children across the globe. On the other hand, IAD is one of the noncommunicable diseases (NCDs) of childhood as we claimed metabolic syndrome for adulthood, and atopic dermatitis causes burdens in health care systems.[21] One study estimated the direct and indirect costs of atopic dermatitis to total over 5 billion dollars annually in the US.[22] The primary prevention of IAD remains a major concern.

Limitations of this study included the short time of follow-up visit, small number of participants, lack

of measurement of skin moisture or TEWL and lack of sensitization tests for allergens. More evidence for the primary prevention of IAD still needs further investigations.

CONCLUSION

This study presented evidence that regular emollient use concomitant with good skin care practice since early infancy could be an effective modality for the primary prevention of infantile atopic dermatitis among high risk infants.

What this study adds

Enhancing the skin barrier by regular emollient use together with implementing good skin care practice for caregivers of infants born in atopic families could serve as a modality for the primary prevention of infantile atopic dermatitis.

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