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Prospective Trial Comparing Topical Steroid Application To Wet Versus Dry Skin In Children With Atopic Dermatitis

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PROSPECTIVE TRIAL COMPARING TOPICAL STEROID APPLICATION TO WET VERSUS DRY SKIN IN CHILDREN WITH ATOPIC DERMATITIS

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ABSTRACT

PROSPECTIVE TRIAL COMPARING TOPICAL STEROID APPLICATION TO WET VERSUS DRY SKIN IN CHILDREN WITH ATOPIC DERMATITIS.

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The aim of this study was to determine whether "soak and smear," a technique where hydration via a 10-minute soak in lukewarm plain water followed by topical corticosteroid application to wet skin, is efficacious for the treatment of atopic dermatitis in pediatric patients. A randomized, investigator-blinded study was conducted with 45 patients, 4 months to 16 years of age, with moderate to severe atopic dermatitis. All patients received fourteen days of topical corticosteroid ointment and were randomly assigned to either apply the corticosteroid on wet skin via the soak and smear method (treatment arm) or on dry skin (control arm). The primary outcome measure was percentage improvement by Eczema Area and Severity Index (EASI) score. Atopic dermatitis severity of patients who applied corticosteroid ointment to wet skin via soak and smear improved 84.8% by EASI score, whereas atopic dermatitis severity of patients who applied corticosteroid ointment to dry skin improved 81.4% by EASI score. There was no statistical difference between the two groups (p-value = 0.85). The use of corticosteroid application to pre-hydrated, wet skin is not more efficacious than corticosteroid application to dry skin in pediatric patients with moderate to severe atopic dermatitis.

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INTRODUCTION

Atopic dermatitis (AD), synonymous with 'atopic eczema' and colloquially referred to as 'eczema', is a chronic, inflammatory skin disease that primarily affects infants and children. AD is one component of an atopic triad, which includes asthma and allergic rhinitis. AD is thought to have a complex pathogenesis involving genetic predisposition leading to a dysfunctional skin barrier and immune dysregulation, and environmental factors that lead to clinical presentation. The hallmark of AD lies in its pruritic nature, which contributes to much of the disease burden shouldered by patients and their families.

Epidemiology

AD is mainly a disease of childhood and is thought to have a prevalence of 10-20% in children and 3-10% in adults in the United States depending on diagnostic criteria (1, 2). The most recent comprehensive United States study derived from the 2003 National Survey of Children's Health reported a point prevalence of AD in children 0-17 years of age ranging from 8.7% to 18.1% by state with the nationwide average being 10.7%. (1) These results are consistent with other United States-based epidemiological studies (3, 4). The wide range of prevalence suggests that environmental influences may play a role in disease expression, and indeed the prevalence was noted to be higher in urban areas (1). AD may affect individuals of all ages, but most commonly begins in childhood: in 60% of cases it begins in the first year of life, and in 85% of cases it begins by 5 years of age (5).

Clinical Manifestations and Diagnosis

Typically, AD is classified into three age-related stages: infantile, childhood, and adulthood. The infantile form, which occurs in children up to 2 years of age, is typified by acute inflammation, which presents as intensely pruritic, red, weeping papules and plaques often

accompanied by vesicles, scale, and serous crust on the cheeks and extensor surfaces. In school age children, AD is typified by chronic inflammation, migrates to flexor surfaces, and presents with less exudation and more hyperkeratotic plaques and papules. It remains intensely pruritic and increased scratching and rubbing result in lichenification and scale. In adults, AD presents similarly to childhood AD, especially in those who had AD in childhood; however, AD in adults has more of a tendency to localize to the hands and eyelids.

In 2003, The American Academy of Dermatology Consensus Conference on Pediatric Atopic Dermatitis published a set of clinical criteria required for the diagnosis of AD. The diagnosis of AD depends on the exclusion of other similar red, scaly pruritic conditions such as scabies, seborrheic dermatitis, allergic or irritant contact dermatitis, ichthyoses, cutaneous T-cell lymphoma, psoriasis, and immune deficiency diseases (6). After the exclusion of other dermatologic conditions, the diagnosis is based on essential, important, and associated features listed in Table 1.

Table 1: Diagnostic Guidelines for Atopic Dermatitis (6)

Essential features *must be present*	Pruritus Eczematous changes • typical morphology: ○ facial, neck, and extensor lesions in infants and children ○ flexor lesions in any age group ○ sparing of the groin and axillary regions • age-specific distributions Chronic or relapsing course
Important features *seen in most cases*	Early age onset Personal/family history of atopy (IgE reactivity) Xerosis

Table 1: Diagnostic Guidelines for Atopic Dermatitis, continued

Associated features *seen often, but nonspecific*	Atypical vascular responses (facial pallor, delayed blanch response) Keratosis pilaris Pityriasis alba Hyperlinear palms Ichthyosis Ocular/periorbital changes Perioral/periauricular lesions Perifollicular accentuation Lichenification Prurigo lesions

Burden of Disease

Because of its high prevalence and non-life threatening status, health care professionals frequently view AD as a minor skin ailment that resolves with age. Yet, living with AD can have a profound impact on quality of life. Both the physical discomfort of AD as well as the psychological distress have been shown by numerous studies to negatively impact patients' health-related quality of life. In fact, when Beattie *et al* compared the quality of life in children with AD against children with other skin diseases and children with other chronic childhood diseases using a standardized questionnaire, the Children's Life Quality Index©, they found that generalized AD impaired quality of life more than diabetes, epilepsy, asthma, cystic fibrosis, and renal disease. In fact, AD scored higher than other common childhood diseases except cerebral palsy (7).

Although this may seem surprising at first, the physical discomfort of AD, consisting mainly of intense pruritus, and its associated illnesses, such as other atopic diseases as well as

bacterial and viral super-infection can lead to restriction of daily activities, limited participation in sports, and decreased social time. Given that AD lesions in children predominantly occur on easily visible areas, like the face, posterior neck, extremities, hands, and feet, the cosmetic consequences of this rash can hinder the development of strong, positive social relations. Other children and teachers may see the weeping red rash, scaly lichenified skin, and/or the excessive scratching of children with AD and alienate them for fear of infection. Embarrassment, comments, teasing and bullying cause poor self-image and self-esteem. In older children, AD lesions may lead to anxiety and depression.

The intense pruritus of AD leads to sleep disturbances, which then leads to daytime drowsiness and an increased struggle to remain focused in the classroom (8). Families, especially parents or caregivers, are substantially affected by sleep deprivation. On average, parents lose 2.7 hours of sleep per night during an AD flare (8). Sleeplessness in turn can hinder caregiver work performance and coping skills in the home. Additionally, the burden of providing treatment, which includes complicated topical regimens, increased laundry, house cleaning, and restrictions on travel cause stress, anxiety, frustration, and hopelessness amongst caregivers. Dysfunctional parent-child relationships occur more frequently with intractable eczema, and may play a role in altering child behavior (9). Moreover, there is a strong correlation between AD and mental health problems in children. Children with AD show increased emotional difficulties, conduct problems, and hyperactivity/inattention that may persist even after clearance of their AD (10).

Theory of Pathogenesis

Traditionally, it had been postulated that a defective epidermal permeability barrier and a proclivity to develop secondary cutaneous infections, two hallmarks of AD, are caused by a hyperactive and dysregulated immune system. However, in 1999 two independent groups

proposed the reverse: they postulated that clinical manifestation of AD develops from a primary disruption of the epidermal barrier (11, 12). Disruption of the natural barrier properties of skin, which could be caused by genetic defects, trauma, infection, and altered pH, exposes cutaneous immune cells to antigens and irritant agents, leading to release of proinflammatory cytokines and causing cutaneous inflammation (13).

A strong genetic basis for the development of AD is suggested by twin studies showing that if one monozygotic twin develops AD, the other has an 80% rate of developing AD, whereas the rate is only 20% in dizygotic twins (14, 15). Patients with AD have been shown to have an array of genetically determined risk factors that impair skin barrier function. To date, the best-studied gene associated with the development of AD is *FLG*, which encodes for filaggrin (16). In normal skin, formation of the cornified cell envelope begins with the dephosphorylation and cleavage of profilaggrin into functional filaggrin monomers. Filaggrin facilitates the collapse and flattening of keratin filaments, which is essential for keratinocyte terminal differentiation. Loss-of-function mutations in *FLG* have been found in 20-50% of European children with AD as compared to 10% of the general European population, with more than half of children with moderate to severe AD possessing a mutation (16, 17).

In addition to decreasing structural integrity of the cornified envelope, the barrier function of the stratum corneum can be damaged by reducing epidermal hydration. A lipid molecule, ceramide, is an essential component in the generation of natural moisturizing factor. Ceramide plays a role in retaining water and its decreased presence in elderly individuals is the main reason for xeroderma of the elderly. In AD, upregulation of sphingomyelin deacylase activity precludes functional ceramide, resulting in the inability of stratum corneum to hold onto water. The stratum corneum is composed of proteins that promote water absorption and lipids that prevent water loss through the epidermis. Both are necessary for epidermal barrier function, and transepidermal water loss results in xerotic

skin, which secondarily causes pruritus prompting scratching, which causes trauma to the skin. Damage to the stratum corneum promotes the release of proinflammatory mediators, leading to more pruritus, and inducing the "itch-scratch" cycle notorious to AD.

Compromise of the skin barrier in turn increases exposure of the immune system to environmental antigens, which is postulated to play a major role in sensitizing and upregulating the immune system in AD. Studies have shown that *FLG* mutations predispose to childhood asthma only in children who first develop AD. In fact, one study has shown that children with *FLG* mutations who develop both AD and food allergy have a 100% positive predictive value for developing asthma (18). This progression of first developing AD and food allergy, then asthma, and finally allergic rhinitis in childhood is known as the atopic march. The main theory behind the atopic march is one based on the observation that more severe AD and skin barrier disruption correlates with higher serum IgE levels. In fact, sustained exposure to antigens through a defective skin barrier leads to a local increase in T-helper 2 (Th2) infiltrate. Th2 cells release cytokines such as IL-4, which further damage the dysfunctional barrier, worsening the cutaneous disease (19). Furthermore, this local response later becomes a systemic immune hypersensitization and leads to the development of asthma and allergic rhinitis.

Treatment Options

Treatment for AD consists of an exhaustive assembly of options that address barrier dysfunction and cutaneous inflammation through either supportive/preventive measures or through pharmacologic therapy.

The level of success attained through supportive care for AD is directly related to how much education patients and their families receive about AD (20). Patients and their families need

to be educated on what environmental factors may trigger AD in order to minimize their contact with them. Triggers will vary among patients, but common trigger factors include alkaline soaps, dust mites, animal dander, wool or rough synthetic fibers, food allergens found in eggs, peanuts, and cow's milk (21). Effective dust mite reduction in the bedroom through high-filtration vacuuming, using protective bedding, and benzyl tannate spray has shown to improve AD modestly (22). An excellent skin care regimen aimed at improving and preventing xerosis is first-line therapy for AD. Generally, the use of emollients consisting of ointments and creams, which contain more lipids, are more effective for skin hydration and improving barrier function than lotions, which are water-based (6). Optimal bathing technique should also be explained as it can be helpful if done correctly: alkaline soaps should be replaced with mild non-alkaline cleansers; cleansers can be used sparingly, only focusing on the groin and axilla, where apocrine glands are found; and baths and showers should be with warm water, not hot water, which may increase inflammation and irritation. Bubble baths and scented salts should be avoided. After bathing, caregivers should gently pat the child dry with a towel taking care not to rub the skin, which can be thought of as scratching. Immediately after towel drying, the liberal quantities of a moisturizer should be applied to avoid allowing moisture from evaporating off the skin.

Oftentimes, supportive and preventative care is adequate at keeping AD at bay. However, a stressful situation such as beginning a new school year may cause a child's AD to flare. In these circumstances, pharmacologic agents may be used to quickly gain control of a disease exacerbation. Topical corticosteroids (see Table 2) are the first line of pharmacologic therapy, and they work through their anti-inflammatory, immunosuppressive, and vasoconstrictive actions (21). During an exacerbation, they are usually applied twice daily, although certain formulations may be applied once daily. More potent corticosteroid ointments like fluocinonide may be used for lichenified plaques, whereas the mid-potency

preparation 0.1% triamcinolone acetonide is frequently prescribed for widespread whole-body application, excluding intertriginous and facial areas. Once control of AD has been achieved, topical corticosteroids may be tapered down to a mid potency preparation and applied twice weekly as a maintenance dose for children with moderate-severe disease.

Table 2: Select Topical Corticosteroids Used in the Pediatric Population

Potency (group)	*Generic*	*Vehicle**
Ultra high (I)	Clobetasol propionate 0.05% Augmented betamethasone dipropionate 0.05%	C, F, O, L O
High (II)	Fluocinonide 0.1%	C
	Mometasone furoate 0.1%	O
Medium to high (III)	Fluticasone propionate 0.005%	O
	Triamcinolone acetonide 0.1%	O
Medium (IV and V)	Prednicarbate 0.1%	C
	Fluticasone propionate 0.05%	C, L
	Mometasone furoate 0.1%	C
Low (VI)	Alclometasone dipropionate 0.05%	C, O
	Desonide 0.05%	C, G, F, O
	Fluocinolone acetonide 0.01%	C
Least potent (VII)	Hydrocortisone 1%, 2.5%	O,C,L

**C = cream; F = foam; G = gel; L = lotion; O = ointment*

Side effects of topical corticosteroids are well known with the most common one being skin atrophy due to their inhibition of collagen synthesis. Higher potencies, occlusion, and areas of thinner skin like the face, neck, and intertriginous areas increase the risk of atrophic changes in the skin such as easy bruising, increased fragility, purpura, striae, and telangiectasia. Other local adverse effects topical corticosteroids may cause are changes in

pigmentation, rosacea, acne, contact sensitization, cataracts, and glaucoma. Systemic adverse effects, while rare, include suppression of the hypothalamic pituitary-adrenal axis, Cushing disease, decreased growth rate, and reduced bone density (21). Although these potential adverse effects may dissuade healthcare providers from prescribing stronger topical corticosteroid formulations, it is important for a topical preparation of adequate potency to be selected for treatment, because long-term use of inadequately potent topical corticosteroids can be equally as harmful as briefly using highly potent corticosteroids and may not completely clear the disease (22).

Immunocompetent children of at least two years of age with frequently flaring or persistent AD that would require continual topical corticosteroid application may be treated with topical calcineurin inhibitors (TCI) instead, because TCIs are not associated with skin atrophy or striae. TCIs have been approved by the United States Food and Drug Administration (FDA) as second-line therapies for children with AD: tacrolimus for moderate-severe AD and pimecrolimus for mild-moderate AD. In 2006, the FDA released a black box warning of the potential risk of cancer with the use of TCIs. This theoretical possibility of malignancy warning was added based on two areas of concern. High dose oral calcineurin inhibitors given as immunosuppression in transplant recipients had been associated with post-transplant lymphoproliferative disorder and nonmelanoma skin cancer. Additionally, mice and primates that were exposed to very high doses of oral calcineurin inhibitors (30-50 times higher levels of systemic calcineurin inhibitors than the recommended oral dosages in humans) developed lymphomas (23). Prospective, long-term safety studies in both children and adults are ongoing for TCI treatment in AD. Thus far, a 10-year prospective safety study of topical tacrolimus in children has not detected an increased incidence of lymphoma or nonmelanoma skin cancer in the 8,000 children that it has enrolled (24).

In AD that is refractory to topical treatments, systemic immunomodulatory therapies such as oral cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil may be used. However, because of their more alarming side effect profiles, they should be reserved for short-term treatment of severe AD that has been recalcitrant to topical treatment. Other alternative therapies include phototherapy, sedating antihistamines at bedtime to break the itch-scratch cycle, and antimicrobials for those with infected AD. Phototherapy risks include sunburn and with long-term use, photo-aging and a theoretical risk of cutaneous malignancies.

Because systemic treatments have such a high side effect profile, several adjunctive techniques have been described to increase the efficacy of standard topical treatments, including wet wraps and soak and smear. The use of wet wraps have been studied in children with severe and/or refractory AD with considerable success (25, 26). The process of applying wet wraps involves first bathing, applying a topical steroid and/or emollient over the body, then wrapping the child first in damp cotton bandages or damp cotton pajamas, and finally in dry cotton bandages or pajamas before bed. Wet wraps increase skin hydration, physically inhibit the ability to scratch, and increase penetration of topical corticosteroids by acting as an occlusive barrier. However, wet wraps need to be applied carefully, as improper technique may result in maceration of the skin and secondary infections (21). There is much reluctance from families and providers to use wet wraps, because the wrappings are tedious to cut down to the correct size, to apply, and perceived as an added expenditure. Older children and adolescents may not tolerate this treatment, seeing it as unattractive, time-consuming, and uncomfortable (27). Additionally, due to the occlusive and wet nature of the wraps, discomfort and chills are to be expected, and folliculitis is a common adverse event. Systemic bioactivity of corticosteroids as defined by prolonged suppression of the hypothalamus-pituitary-adrenal cortex axis and growth retardation has

not been reported in the published literature after short-term (2-14 days) intervention wet wrap treatment (28).

Similar to wet wraps, soak and smear focuses on aggressively hydrating the skin, removal of scale and crust, and increasing the delivery of topical corticosteroids by application to wet skin. Soaking functions to aid in exfoliation and creating a thinner and a more hydrated stratum immediately prior to topical corticosteroid application. Smearing immediately after soaking presumably functions to trap moisture in the already wet stratum corneum and enhance delivery of the topical medication. Studies have shown that higher levels of topical medications penetrate the dysfunctional epidermal barrier of AD than normal fully functional epidermal barrier (29). Additionally, topical medication penetrates moist stratum corneum 10-100 times more than dehydrated stratum corneum (30). In contrast to wet wraps, soak and smear does not provide a physical barrier to scratching or act as an occlusive barrier. Although time intensive and messy, it is less so than wet wraps, as it cuts out the necessary steps of acquiring appropriately sized cotton bandages or pajamas, wetting them, and wrapping them around the child. Soak and smear treatment has been shown to be highly effective in two studies in adults, one retrospective and one prospective.

Previous Publications on Soak and Smear

The first published report using the term “soak and smear” was a retrospective study of 28 adults with difficult to treat eczema (approximately half with AD) who were instructed on the soak and smear protocol and underwent at-home nightly soak and smear therapy for a minimum of four days and a maximum of two weeks until their eczema had cleared. Of the 28 patients, 17 showed complete clearance, 9 showed more than 90% clearance, and 2 showed more than 75% clearance. After soak and smear treatment was discontinued,

patients were tapered down to applying ointment on without prior soaking, and finally to twice daily application of emollients (30). No long-term follow up was reported.

In the second prospective study, seven deployed patients in the combat setting with severe flares of AD that had failed standard AD treatments underwent twice daily soak and smear for three days in the hospital setting using triamcinolone ointment over the entire body sparing the face and intertriginous areas. At the end of three days, they were discharged and instructed to continue twice daily smears without prior soaking for 11 days. On days 0, 2, 7, and 14 they were evaluated by investigators for total body surface area affected, investigator global assessment (IGA) score, and patient self-assessment of AD and pruritus. Overall, more than 90% of patients responded with 90-100% clearance of disease. All patients were noted to have substantial improvement by day 2 with a mean score of 1 on the IGAS as compared to a mean score of 4 on day 0. Improvement in IGA score, patient self-assessment of disease severity, and patient self-report of pruritus improved over the first seven days of treatment, and remained the same from day 7 to day 14 (31).

Rationale

To our knowledge, only two studies have investigated the efficacy of soak and smear for AD, both of which are described above and neither of which have studied soak and smear in the pediatric population. Current application of soak and smear in the pediatric population is based primarily upon evidence from its success in the adult population, anecdotal reports, and expert opinion. Only wet wrap dressings, which are similar in proposed mechanism of action to soak and smear, have been studied in the pediatric population, and their efficacy, although significant, has been less dramatic than what has been seen with soak and smear in the adult population. In addition, wet wraps are tedious to apply and may encourage noncompliance and cause more stress to families and patients than soak and smear. For

this reason, we believe that soak and smear may be a highly effective method of quickly gaining control of atopic dermatitis flares.

STATEMENT OF PURPOSE

Primary Aim

The primary aim of this study was to compare the efficacy of a soak and smear regimen for the application of topical corticosteroid ointment to the application of corticosteroid ointment applied without prior soaking (control) in children with atopic dermatitis. The hypothesis was that the soak and smear regimen would be more efficacious than the control regimen for the treatment of atopic dermatitis in children. Study subjects were less than 18 years of age, and the protocol included triamcinolone acetonide 0.1% ointment for patients 2 years of age or older or hydrocortisone 2.5% ointment for patients less than 2 years of age. For patients in the experimental group, topical medication was applied to the face and intertriginous areas twice daily, once with soak and smear regimen and once without; control patients did not undergo the soaking procedure. Efficacy was calculated using percentage improvement by the Eczema Area Severity Index (EASI) and by patient or caregiver assessment of disease severity and pruritus.

Secondary Aims

Secondary aims for this study were to investigate the influence of corticosteroid ointment application by soak and smear regimen versus standard regimen on hypothalamic-pituitary-adrenal axis suppression and to quantify the level of corticosteroid ointment penetration through the skin by each regimen through serum cortisol levels.

Additionally, this study sought to evaluate adverse events in each arm to determine if there would be any increased potential for harm in applying the medication employing the soak and smear regimen.

METHODS

Contributors' Statement

Lucinda S. Liu designed and coordinated the study, collected data, and contributed to data analysis. Yanna Kang analyzed the data. Richard J. Antaya conceptualized and designed the study and contributed to data analysis.

Study Design

Patients two years of age or older were prescribed topical triamcinolone acetonide 0.1% ointment twice daily, and patients younger than two years of age were prescribed hydrocortisone 2.5% ointment twice daily. All patients were prescribed hydrocortisone 2.5% ointment for facial and intertriginous areas. This medication regimen was part of the age-appropriate standard of care healthcare provided to pediatric AD patients treated in the Yale Pediatric Dermatology Clinic. Patients were randomized for method of application for the topical ointment. The soak and smear arm employed the soak and smear regimen only during the evening application of corticosteroid ointment.

If a patient was undergoing any treatment that requires the use of systemic corticosteroids, topical corticosteroids, or antibiotics, a washout period in which the medication was discontinued was required of the patient prior to participating in the study. A washout period of two weeks was required if the patient was undergoing systemic corticosteroid therapy. A washout period of one week was required of any patients who were undergoing topical corticosteroids therapy or systemic antibiotic treatment.

The primary endpoint was the change in EASI score. The secondary endpoints were the patient's/guardian's evaluation of disease severity, impact on sleep, and itch, adverse

effects reported by the patients/guardians or observed by the medical staff, and AM serum cortisol levels.

Eligibility Criteria

Patients were required to meet the following eligibility criteria:

1. Patients must meet the clinical criteria of the American Academy of Dermatology Consensus Conference on Pediatric Atopic Dermatitis for the diagnosis of AD and have disease over at least 5% of their total body surface area.

2. Patients less than 18 years of age.

3. Families able to comprehend written instructions in English and able to complete questionnaires with assistance if needed.

4. Parents/guardians able to understand and willing to sign a parental permission form. Children between the ages of 7-17 years will sign an age-appropriate assent form.

Exclusion Criteria

Patients who met any of the follow exclusion criteria were excluded from the study:

1. Clinically infected AD.

2. Patients who were allergic or intolerant of triamcinolone 0.1% ointment or hydrocortisone 2.5% ointment.

3. Patients who did not have access to a bathtub.

Blinding

The trial was blinded to Lucinda Liu who was responsible for all patient evaluations. Richard Antaya, MD was not blinded and was responsible for demonstrating application of the drug to the patients or parents/guardians. In order to maintain the blind, both the patient and the parent/guardian were instructed not to discuss the prescribed regimen with the blinded investigator.

Randomization

Patients were randomized in a form of restricted randomization known as random permuted blocks in which patients were randomized in blocks of either length four or six. This allowed for the patients to be randomized maximally while maintaining a relatively equal number of participants in each arm. In addition, because the blocks were of different lengths, and the lengths were randomized, there was less likelihood of the blinded investigator being able to predict the treatment regimen of the last patient in the block in the unlikely event that the blinded investigator was able to determine which patients were assigned to each arm for patients in a block (32).

Treatment Administration

Treatment was administered on an outpatient basis. On Day 0, all patients underwent a baseline history, which included demographic data, medical history, medication list, and personal and family history of AD, food allergies, asthma, and allergic rhinitis; physical exam; scoring of AD using EASI score, a patient self-assessment of disease severity and pruritus; and standardized digital photography of affected areas of the skin.

All patients received a one-page handout that briefly explains AD and educates families on how to prevent further atopic dermatitis outbreaks (Appendix 1: Educational Hand-out). The soak and smear arm received a page explaining the theory behind soak and smear and be given instructions on how to perform the soak and smear regimen (Appendix 2: Soak and Smear Instructions). The control arm received a page explaining how to apply corticosteroid ointment for treatment of AD and specific instructions on bathing which requested caregivers to refrain from applying the topical corticosteroid to wet skin (Appendix 3: Standard Regimen Instructions).

Patients/caregivers completed their therapies at home and documented progress, level of pruritus, level of sleep deprivation, and compliance at home daily in a handout that was provided to them at the initial visit (Appendix 3: Guardian Check Sheet).

Both arms adhered to their respective regimens for two weeks, and then was assessed for clearance of AD. For those patients in the standard regimen arm, if the patient's AD had less than 75% clearance by EASI score, patients and their families/caregivers were offered to cross over into the soak and smear arm, and began the study again at Day 0 with a new baseline assessment followed by two weeks of the soak and smear regimen. If the patient's AD had more than 75% clearance by EASI score, patients and their families/caregivers

began maintenance therapy, which consisted of emollients and soap-free cleansers for bathing, and avoidance of harsh chemical detergents and fabric softeners.

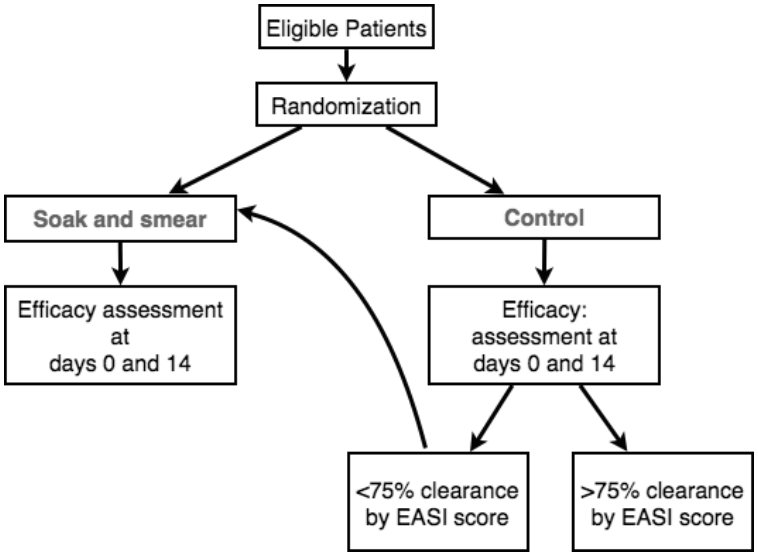

Figure 1. Distribution of Patients

Data Collection and Outcome Measures

Assessment of AD by EASI score was conducted by the blinded investigator at baseline on Day 0 and Day 14 at the Yale Pediatric Dermatology Clinic.

The main outcome measured was efficacy by EASI, which assessed AD disease severity based on level of dermatitis and body surface area involvement (33). The EASI is based on four key aspects of AD that encompass both acute and chronic disease: erythema, induration/papulation, excoriation, and lichenification. These aspects are scored and then weighted by the proportion of body surface area affected. The EASI was chosen as the objective measurement of disease, because it has exhibited good inter-evaluator consistency, validity, sensitivity to change and correlated well with other validated measures of AD severity, such as the SCORAD (34).

The EASI assessment does not place value in any subjective measures of disease, such as level of pruritus or sleep loss. In turn, itch score, overall impact of disease, and compliance were recorded by the patient or caregiver at daily at home for the following 14 days. On Day 14, patients and their caregivers returned to the Yale Pediatric Dermatology Clinic, and were asked to report adverse effects. Digital photographs utilizing the same standard poses as baseline were also taken at this time.

Patients and families that volunteered for giving blood samples were asked to submit a blood sample on Day 14. On Day 0, all patients who have agreed to the blood draw were offered topical anesthetic (lidocaine 2.5%-prilocraine 2.5% cream) for application to the antecubital fossae one hour prior to the blood draw on Day 14 to decrease procedural discomfort. Blood samples were drawn by phlebotomists at the Yale Center for Clinical Investigation (YCCI) laboratory. Per the YCCI protocol, 1 ml of blood was drawn by venipuncture and stored in a lavender tube containing dipotassium ethylenediaminetetraacetic acid. Blood samples were sent to the YCCI Core Laboratory Services, and serum cortisol levels were processed in one batch by enzyme-linked immunosorbent assay using a radioimmunoassay kit. Normal AM serum cortisol values were set by the manufacturer as 5-25 ug/dL (138-690 nmol/L).

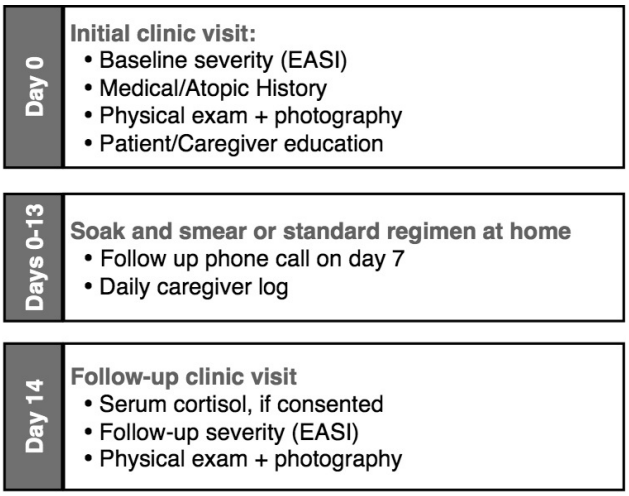

Figure 2. Data Collection Flowchart

Sample Size Calculation

To calculate our sample size, our null hypothesis was that there would be no difference in treatment results between the two arms. Predicted outcome for the soak and smear arm, which was measured by percentage improvement, was estimated from the two previous studies on soak and smear:

Rustad and Henning (31)

4 patients improved 100%

1 patient improved 80%

1 patient improved 75%

1 patient improved 67%

mean improvement=88.9%

Gutman *et* al (30)

17 patients improved 100%

9 patients improved 95%

1 patient improved 80%

1 patient improved 75%

mean improvement=96.8%

From this, a weighted average of 95.2% improvement for the arm using soak and smear was calculated. The predicted outcome size for standard treatment was estimated using a previous study that cited 60.5% improvement in patients with AD who applied triamcinolone 0.1% ointment to dry skin twice daily for two weeks. From this, the predicted effect size, defined as a difference in mean of outcome variables between two arms, was calculated to

be 35%. The standard deviation was then calculated to be 13.3 / (47.6 – 18.8) = 0.45. From this, the standardized effect size was calculated by dividing 35 by 45, which is 0.78.

For this study to detect a difference of at least 15% (by objective EASI score) between the two treatment arms, with an estimated standard deviation of 20%, and using a two-sided *t* test with α (two-sided)=0.05, we required a sample size of 26 participants in each arm to reach 80% power (35). Estimating a drop out rate of 5%, we calculated a need for 55 participants total to reach significant power.

Statistical Analysis

A two-sided Wilcoxin rank sum test was used over the unpaired t-test for the following reasons: the subjects of the two arms are independent samples but cannot be assumed to be normally distributed, and the sample size is small (36). The null hypothesis was that the mean percentage improvement by EASI score in the treatment arm (soak and smear) is the same as that in the control arm. Whereas, the alternative hypothesis was that the mean percentage improvement by EASI score in the two arms are different. The formula used to calculate mean percentage difference by EASI score is as follows: if patient A scored an initial EASI score of A1 and a final EASI score of A2, and patient B scored an initial EASI score of B1 and a final EASI score of B2, the mean percent age difference was calculated by the formula [(A1 – A2)/A1 + (B1 – B2)/B1]/2.

Investigative Review Board Approval and ClinicalTrials.gov Registration

This study was approved by the Yale Pediatric Protocol Review Committee and Yale Human Research Protection Program (HRPP), formerly known as the Human Investigation Committee of Yale School of Medicine, in June 2012. This study was also posted on ClinicalTrials.gov in August 2012 and has the identifier NCT01675232.

RESULTS

Demographics and Baseline Comparisons

Between July 2012 and July 2013, 46 patients with atopic dermatitis presented to the Yale Pediatric Dermatology clinic who were eligible for our study. Of these, 45 patients enrolled in our study. Every patient had been referred from either their general pediatrician or community dermatologist.

Table 3: Demographics

	CONTROL	SOAK AND SMEAR	Wilcoxin
Patients	23	24	
Age in years *mean ± SD (range)*	3.1 ± 4.0 (0.3 - 16)	3.2 ± 3.4 (0.3 - 11)	p = 0.8
Gender female : male	8 : 15	10 : 12	p = 0.18*
Race			p = 0.28**
Caucasian	14	12	
Black	2	5	
Asian	5	2	
Hispanic	0	2	
Other	2	1	
Initial EASI *mean ± SD (range)*	15.1 ± 6.9 (2.8, 29.7)	15.8 ± 9.1 (4.6, 34.95)	p = 0.9

*p-value calculated by Fisher's exact test. **p-value calculated by chi-square test.

All 45 patients, 22 in the soak and smear arm and 23 in the control arm, returned for their 14-day follow-up visit. Two patients were originally enrolled in the control arm and subsequently crossed over into the soak and smear arm after two weeks of treatment. Patients ranged from 4 months of age to 16 years of age, with an average of 3.2 and 3.1 years of age in the soak and smear and control arms, respectively. The mean EASI score was 15.8 and 15.1 in the soak and smear and control arms, respectively. Demographic characteristics are further delineated in Table 3.

Efficacy by Eczema Area and Severity Index

Patients in the soak and smear arm showed a mean reduction in EASI score from baseline of 84.8% ± 16.5%, from a mean initial EASI score of 15.8 ± 9.1 to a mean final EASI score of 2.5 ± 3.5 at the two-week visit. Patients in the standard arm showed a mean reduction in EASI score from baseline of 81.4% ± 25.6%, from a mean initial EASI score of 15.1 ± 6.9 to a mean final EASI score of 2.6 ± 4.3 at the two-week visit. There was no difference between the soak and smear arm and the standard treatment arm (p = 0.85) (Table 4).

Table 4: Outcomes by EASI Score

	INITIAL EASI *mean ± SD (range)*	FINAL EASI *mean ± SD (range)*	% DIFFERENCE *mean ± SD (range)*	Wilcoxin
CONTROL	15.1 ± 6.9 (2.8, 29.7)	2.6 ± 4.3 (0, 19.1)	81.4 ± 25.6 (0.5, 100)	p = 0.85
SOAK AND SMEAR	15.8 ± 9.1 (4.6, 34.95)	2.5 ± 3.5 (0, 13.5)	84.8 ± 16.5 (40.2, 100)	

Given that there was no statistically significant difference in outcome by EASI score between the soak and smear and standard treatment arms, the question was asked whether the soak and smear method would benefit patients with more severe AD. The two arms were then stratified into mild, moderate, and severe subgroups by EASI score, which was adopted from a previously published stratification model by Eichenfield *et* al (37). Patients with EASI scores of 8 or less were categorized as mild; those with EASI scores of greater than 8 to 15 were categorized as moderate; and those with EASI scores of greater than 15 were categorized as severe. Overall, nine patients were stratified into the mild AD subgroup by their initial EASI score, of which four patients were randomized to the soak and smear arm. Twenty patients were stratified into the moderate AD subgroup by their initial EASI score, of which nine were randomized to the soak and smear arm. Finally, eighteen patients were stratified into the severe AD subgroup by their initial EASI score, of which nine were randomized to the soak and smear arm.

Patients who had severe AD and who were randomized to the soak and smear arm showed a mean reduction in disease severity of 83.0% ± 19.4% by EASI score. Patients who had severe AD and who were randomized to the control arm showed a mean reduction in disease severity of 80.9% ± 32.7% by EASI score. Once again, there was no statistically significant difference between the two treatment arms for those with severe AD ($p = 0.39$) (Table 5).

Patients who had moderate AD and who were randomized to soak and smear showed a mean reduction in disease severity of 84.4% ± 17.0% by EASI score. Patients who had moderate AD and who were randomized to control showed a mean reduction in disease severity of 81.9% ± 24.0% by EASI score. There was no statistically significant difference between the two treatment arms for those with moderate AD ($p = 0.57$) (Table 5).

Patients who had mild AD and who were randomized to soak and smear showed a mean reduction in disease severity of 89.7% ± 9.2% by EASI score. Patients who had moderate AD and who were randomized to control showed a mean reduction in disease severity of 81.1% ± 7.95% by EASI score. There was no statistically significant difference between the two treatment arms for those with mild AD (p = 0.23) (Table 5).

Table 5: Outcomes by EASI Score Stratified by Disease Severity

		INITIAL EASI *mean ± SD (range)*	FINAL EASI *mean ± SD (range)*	% DIFFERENCE *mean ± SD (range)*	Wilcoxin
Severe AD	CONTROL	22.2 ± 4.2 (16.6, 29.7)	3.99 ± 6.4 (0.15, 19.1)	80.9 ± 32.7 (0.52, 99.5)	p = 0.39
	SOAK AND SMEAR	25.2 ± 5.95 (15.35, 34.95)	4.2 ± 4.8 (0.5, 13.45)	83.0 ± 19.4 (40.2, 97.96)	
Moderate AD	CONTROL	11.9 ± 2.3 (8.7, 14.95)	2.0 ± 2.3 (0, 7.9)	81.9 ± 24.0 (14.1, 100)	p = 0.57
	SOAK AND SMEAR	10.5 ± 2.0 (8.1, 15)	1.6 ± 1.7 (0, 4.8)	84.4 ± 17.0 (48.7, 100)	
Mild AD	CONTROL	5.6 ± 2.4 (2.8, 7.35)	0.93 ± 0.28 (0.75, 1.25)	81.1 ± 7.95 (73.2, 89.1)	p = 0.23
	SOAK AND SMEAR	6.3 ± 1.8 (4.6, 7.9)	0.74 ± 0.75 (0, 1.75)	89.7 ± 9.2 (77.6, 100)	

Efficacy as Measured by Pruritus

During the 14-day treatment, each caregiver or patient was instructed to assign a daily value to the patient's level of pruritus on a scale of 0 to 10, with 0 indicating no itch and 10 indicating severe itch. Patients in the soak and smear arm had a mean baseline itch score of 6.3 ± 2.9, which improved by 39.0% ± 91.7% to 2.9 ± 2.3 by Day 7 and by 77.8% ± 20.6% to 1.6 ± 1.9 by Day 14. Patients in the standard treatment arm had a mean baseline itch score of 5.4 ± 3.0, which improved by 48.8% ± 44.6% to 2.7 ± 2.7 on Day 7 and by 75.8% ± 28.0% to 1.9 ± 2.8 by Day 14. There was no statistically significant difference in itch improvement level between the two treatment arms on Day 7 ($p = 0.83$) or Day 14 ($p = 0.85$) (Table 6).

Table 6: Outcomes by Pruritus Score

	DAY 1 *mean ± SD*	DAY 7 *mean ± SD* *(% diff ± SD)*	Wilcoxin	DAY 14 *mean ± SD* *(% diff ± SD)*	Wilcoxin
CONTROL	5.4 ± 3.0	2.7 ± 2.7 (48.8 ± 44.6)	p = 0.83	1.9 ± 2.8 (75.8 ± 28.0)	p = 0.85
SOAK AND SMEAR	6.3 ± 2.9	2.9 ± 2.3 (39.0 ± 91.7)		1.6 ± 1.9 (77.8 ± 20.6)	

Efficacy as Measured by Overall Impact of Disease

During the 14-day treatment, each caregiver or patient was instructed to assign a daily value to the overall impact of disease, which was explained to each patient and caregiver as how much the AD affected sleep, itch, appearance, and overall quality of life, and was rated on a scale of 0 to 10, with 0 indicating no effect on quality of life and 10 indicating a miserable quality of life due to AD.

Patients in the soak and smear arm had a mean baseline overall impact of disease score of 7.2 ± 2.1, which improved by 52.3% ± 34.3% to 3.1 ± 1.9 by Day 7 and by 64.8% ± 44.0% to 2.2 ± 2.7 by Day 14. Patients in the standard treatment arm had a mean baseline overall impact of disease score of 5.0 ± 3.0, which improved by 54.1% ± 35.7 % to 2.9 ± 2.6 on Day 7 and by 74.0% ± 28.7% to 2.0 ± 2.6 by Day 14. There was no statistically significant difference in impact of disease score improvement between the two treatment arms on Day 7 ($p = 0.8$) or Day 14 ($p = 0.6$) (Table 7).

Table 7: Outcomes by Overall Impact of Disease

	DAY 1 *mean ± SD*	DAY 7 *mean ± SD* *(% diff ± SD)*	Wilcoxin	DAY 14 *mean ± SD* *(% diff ± SD)*	Wilcoxin
CONTROL	5.0 ± 3.0	2.9 ± 2.6 (54.1 ± 35.7)	p = 0.8	2.0 ± 2.6 (74.0 ± 28.7)	p = 0.6
SOAK AND SMEAR	7.2 ± 2.1	3.1 ± 1.9 (52.3 ± 34.3)		2.2 ± 2.7 (64.8 ± 44.0)	

Efficacy as Measured by Sleep

During the 14-day treatment, each caregiver or patient was instructed to assign a daily value to the overall quality of sleep, which was rated on a scale of 0 to 3, with 0 indicating that the patient slept well and 3 indicated that the patient slept poorly.

Patients in the soak and smear arm had a mean baseline sleep score of 1.3 ± 1.1, which improved by 59.0% ± 40.0% to 0.6 ± 0.8 by Day 7 and by 62.5% ± 43.9% to 0.5 ± 0.7 by Day 14. Patients in the standard treatment arm had a mean baseline sleep score of 1.3 ± 1.1, which improved by 54.7% ± 59.4% to 0.7 ± 0.7 by Day 7 and by 54.4% ± 48.2% to 0.7 ± 0.8 by Day 14. There was no statistically significant difference in sleep score improvement between the two treatment arms on Day 7 (p = 0.9) or Day 14 (p = 0.7) (Table 8).

Table 8: Outcomes by Sleep Score

	DAY 1 *mean ± SD*	DAY 7 *mean ± SD* *(% diff ± SD)*	Wilcoxin	DAY 14 *mean ± SD* *(% diff ± SD)*	Wilcoxin
STANDARD	1.3 ± 1.1	0.7 ± 0.7 (54.7 ± 59.4)	0.9	0.7 ± 0.8 (54.4 ± 48.2)	0.7
SOAK AND SMEAR	1.3 ± 1.1	0.6 ± 0.8 (59.0 ± 40.0)		0.5 ± 0.7 (62.5 ± 43.9)	

Compliance

During the two weeks of study participation, patients were relatively compliant to their topical corticosteroid application regimens. This was recorded on the caregiver worksheet, which asked caregivers or patients to record on a daily basis whether or not they were able to adhere to the treatment intervention. On average, patients randomized to the soak and smear arm missed 0.67 ± 1.09 days of the 14-day intervention. In comparison, patients randomized to the control arm missed on average 0.48 ± 0.59 days of topical corticosteroid application. There was no statistically significant difference between the compliance rate of the two study arms (p = 0.8) (Table 9).

Table 9: Study Compliance

	Mean Number of Days missed ± SD	Wilcoxin
CONTROL	0.48 ± 0.59	p = 0.8
SOAK AND SMEAR	0.67 ± 1.09	

Serum Cortisol Levels

Of the 45 patients enrolled, ten elected to participate in a voluntary AM serum cortisol level draw. All patients had their blood drawn between 8:15 AM and 8:45 AM. Nine of the patients had AM serum cortisol levels within the normal range (Table 10). One patient, who was in the standard treatment arm, had a serum cortisol level of 4.75 ug/dL, which is under the lower limit of normal (5 ug/dL).

Table 10: AM Serum Cortisol Levels

	STANDARD	SOAK AND SMEAR	Wilcoxin
AM Cortisol (ug/dl)	12.35 (4.75 - 22.15)	14.98 (7.01 - 21.47)	p = 0.61

Adverse Events

Three patients in the soak and smear arm and five patients in the standard treatment arm developed folliculitis. No patients in this study developed visible signs of skin atrophy, such as wrinkling, thinning or depression, increased venous pattern, striae, or increased skin fragility. No patients in this study developed any other local adverse effects such as rosacea, acne, contact dermatitis or changes in pigmentation. No patients developed signs of systemic suppression of the hypothalamic pituitary adrenal axis, such as moon facies, fat redistribution, signs or symptoms of glucose intolerance or immunosuppression.

Early Termination of the Study

Although every attempt was made to recruit to our original sample size of 52 patients, our study was terminated early due to investigator-related constraints on time. We were reassured in ending our study at 45 patients after re-estimation of the sample size by

calculating a futility assessment with conditional power (38, 39). The calculated conditional power was calculated based on data gathered after accruing 45 patients. From these data, the conditional power was calculated to be 0.05, which means that, given the data we have accrued so far, there was only 5% chance of rejecting the null hypothesis and concluding that there is statistically significant difference between the two arms. From these conclusions, we found it unnecessary to recruit 52 patients suggested by our original power calculation and terminated the study after recruiting 45 patients.

Crossover Group

Three patients were asked to cross over from the control arm into the soak and smear arm due to a clearance by EASI score of less than 75%, and of those, and of those, two returned for their second 14-day follow-up visit. The family who did not return reported difficulty in keeping the follow-up appointment due to parent work schedule and frustration with lack of AD clearance. Of the two who followed up after crossing over, one improved with 98% clearance, and one improved with 27% clearance in AD severity.

The data was reanalyzed with the addition of the data from the two patients that had crossed over from the control arm into the soak and smear arm. All of the above results remained similar in that there remained no change in statistical significance between the two arms.

DISCUSSION

This study shows that twice-daily application of topical corticosteroid ointment over a period of two weeks results in a considerable improvement in AD severity using either soak and smear or standard topical corticosteroid application techniques. In the two arms studied there was no difference in the degree of AD improvement by EASI score, pruritus, or overall impact of disease at two weeks. Moreover, there was no difference between the two interventions in the more severe AD subgroup or in the moderate AD subgroup.

The Theory of Soak and Smear

Atopic dermatitis is the most common inflammatory skin disease in children, and its pathology is thought to arise from a defect in skin barrier and abnormal immune responsiveness. In theory, soak and smear seems like an effective intervention, combining both intensive hydration to repair the barrier with topical corticosteroid medication to reduce inflammation. Furthermore, soaking effectively exfoliates the skin, which then aids topical corticosteroid penetration. Smearing on ointments then traps the moisture in the stratum corneum and delivers the anti-inflammatory medication where the disease is located. It is this theory that has led to soak and smear's wide acceptance by the dermatology community for treatment of AD and other dermatitis in adults and children despite the limited rigorous studies on its efficacy and absence of studies on its efficacy in the pediatric population. The two studies that were previously published on the efficacy of soak and smear for AD, although promising in their support of soak and smear for recalcitrant AD, were limited in their design.

Limitations of Previous Studies on Soak and Smear

The Gutman *et* al study published in 2005 was retrospective, and as all retrospective studies are in their nature, it was not controlled. For example, length of intervention ranged from several days to two weeks and the method of assessing AD severity and improvement was not a well-validated rubric (only by an undefined "percent response" as rated by both the physician and patient). The intervention in this study was identical to the one we enacted in ours: one nightly soak in lukewarm plain water prior to topical corticosteroid application to wet skin. Additionally, all the patients in this study were adults with ages that ranged from 24 to 84 years of age, which does not translate well to the pediatric population that carries the burden of disease in AD. Finally, only 15 of 28 patients had AD, whereas the others had psoriasis, xerotic eczema, nummular eczema, and irritant dermatitis.

A prospective study conducted by two physicians in the army was subsequently conducted and verified the successful results of the 2005 retrospective study. In this study, seven deployed soldiers in the combat setting who had severe recalcitrant AD who had failed outpatient topical corticosteroids were hospitalized for three days and underwent soak and smear intervention twice daily. This intervention differed from the one in our study, because it was a twice daily soak rather than one nightly soak. Several confounders interfered with the validity of the study results claiming that soak and smear was more effective than standard therapy. First, all seven patients were removed from their combat setting, which was likely a stressful situation to be in and filled with combat debris, and were moved to a controlled hospital setting away from the stress and allergens associated with combat. Previous studies have shown that hospitalization alone may improve the severity of AD (40). Patients in this study underwent direct observed therapy in the hospital setting, another intervention that was not available while the soldiers were in the combat setting. Like the

Gutman *et* al study, there was no control arm in this study, which makes it difficult to conclude that soak and smear is superior to standard treatment. Finally, in both studies, patients were newly referred to these providers, which raises the question of whether it was the care of a new provider or the soak and smear intervention itself that motivated dermatitis clearance.

It is possible that the remarkable improvement in disease severity in both prior studies is truly attributable to the soak and smear intervention and that soak and smear simply does not apply as well to the pediatric population. The patients in these prior studies all reported failing multiple treatments and having recalcitrant skin disease. They were also older and most likely had drier skin than most pediatric AD patients. It could be postulated that soak and smear is an effective intervention for specific populations, namely those with severe disease that is proven to be recalcitrant to adequate topical corticosteroid therapy and/or those with xerotic forms of pruritic dermatitis such as those patients with filaggrin mutations such as ichthyosis vulgaris. This trial did not take into account the presence of ichthyosis vulgaris in our subjects.

Treatment Adherence and the Role of Patient Education

The negative results of this study may initially seem unexpected given the overly positive results of the previous two studies described above as well as the wide acceptance of using soak and smear as a treatment technique for AD. There are several reasons that may explain why the patients who participated in both arms improved remarkably and at the same percentage by EASI score. All of our families benefitted from careful patient education regarding appropriate preventive and therapeutic measures. Preventative measures included proper skin lubrication during non-flared states, removal of irritants in the environment such as non-cotton clothing and bedding, and removal of irritant detergents, all

of which serves to prevent future AD flares. Education regarding therapeutic measures to control current AD flares was mainly geared towards application of sufficient volume of topical corticosteroid medication and maintaining the correct duration of treatment.

Nearly all of our patients presented to our clinic with some level of reluctance towards using adequate amounts of topical corticosteroids. It was clear when caregivers would describe the quantity of topical corticosteroid they had applied under the direction of their previous health provider, that they were not applying sufficient quantities of medication to their affected skin. This is not surprising, since studies have shown that 60-73% of patients or parents have a fear of or anxiety towards using topical corticosteroids, which subsequently leads to under-treatment and poor treatment adherence (41, 42). This phenomenon, referred to by some as "topical corticosteroid phobia," is thought to stem from misunderstanding about the nature of topical corticosteroids. Media publicity, misconceptions that corticosteroids are related to anabolic steroids, and excessive precaution from primary care providers often will lead patients to use inadequate volume of topical corticosteroids or to simply avoid treatment with topical corticosteroids. As with all misconceptions, the most effective method to address them is with education. Although many of our participants initially presented with a fear of using topical corticosteroids, all of them were willing to treat with appropriate volume of topical corticosteroids and for the full treatment duration of two weeks once they received the appropriate education.

Moreover, a great amount of information is exchanged during the clinic encounter, and the method in which teaching is conveyed is also important for patient/caregiver education. In an effort to encourage treatment adherence, patients received both verbal in-person teaching about maintenance and flare treatment of their AD, but also written handouts with the same information. Written action plans have been shown to increase adherence and decrease the number of visits to the emergency department in children with asthma;

however, no studies have looked at the utility of written action plans for children with AD (43). Theoretically, a written hand-out reiterating important treatment concepts is critically important to patient care as it communicates the same information in a different method, clarifies common questions caregivers may have, reminds families to participate in treatment, and helps them navigate changes in treatment. Several studies have shown that time spent educating patients and their caregivers decreased disease severity and improved quality of life (43).

In addition to careful education on the benefits and adverse effects associated with the use of topical corticosteroids for the treatment of AD, our patients were also provided with ample amount of topical corticosteroids. This most likely played a huge role in AD disease clearance as it has been shown that patients who apply the correct amount of topical corticosteroid to AD skin showed a statistically significant improvement in disease severity (44). While not directly measured in this study, it was observed that the majority of subjects referred to the pediatric dermatology clinic with AD had been prescribed an amount of topical steroid insufficient to successfully cover the affected areas for a 2-week course. When insurance policies would allow it and pharmacies had it in stock, patients used one-pound jars of hydrocortisone 2.5% or triamcinolone 0.1% ointment. When one-pound jars were not available due to financial or supply reasons, patients were still given a one-pound equivalent of corticosteroid ointment via multiple tubes. Patients were provided with an estimate as to how much corticosteroid ointment they should have applied by the end of the two-week study intervention, adding further incentive to adhere to the appropriate topical corticosteroid regimen.

Lastly, our patients were very compliant with our recommended treatment schedule and amount of topical corticosteroid applied, which contradicts previous studies showing that pediatric patients with AD are in fact very noncompliant with therapy. For example, a 2007

study using microprocessor stealth monitoring of medication use showed an abysmal 32% adherence to therapy (45). Our study's remarkably high compliance could be due to a variety of factors. The biggest one is the Hawthorne effect: by their being in a study, our patients knew that they were being observed and changed their behavior to accommodate. Additionally, in this study, every patient was called after one week to assess for adverse effects but to also encourage compliance (46). Finally, it has been shown that patients become more adherent to treatment before and after a visit to the doctor. The short follow-up time of two weeks in our study also likely encouraged treatment adherence.

Adverse Effects

The systemic absorption of steroids and possible effects on the hypothalamic-pituitary-adrenal axis is negligible for a two-week time span. Although many clinicians have postulated that a fully hydrated epidermis allows for better penetration of topical medications, in our experience, a well-hydrated epidermis followed by liberal application of topical corticosteroids did not result in suppression of the adrenal axis.

Study Limitations

The biggest limitation of the study was due to study participant number. Our initial power calculation suggested that we would need 52 total participants, yet we only recruited 45 patients. This was mainly due to slower than expected recruitment, but also because of the results of an interim analysis. Additionally, this study's small numbers limits its ability to detect a subset of the population who might have benefitted from soak and smear, as shown by the patient in the crossover group who cleared remarkably with soak and smear, but did not with standard treatment. It would be difficult to draw any conclusions from the characteristics of the three patients in the crossover group given their small number;

however, in looking back through their photos, none of them had ichthyosis vulgaris. Further, given its limited numbers, it would have been difficult to stratify our patients by such traits like very severe AD and ichthyosis vulgaris in an effort to confirm, isolate, and characterize a population that could benefit from soak and smear.

It should also be noted that patients in the soak and smear arm underwent the soak and smear regimen only once per day in the evenings and applied topical corticosteroid to dry skin in the mornings. Thus, it cannot be concluded that performing the soak and smear regimen twice daily would be superior to twice daily control regimen.

Finally, although caregivers were thoroughly educated on how to practice soak and smear, no clinician or study coordinator directly observed the soak and smear therapy regimen. Children can often be energetic and mobile during bathtime, and may not be able to soak themselves in a bathtub as thoroughly and consistently as an adult would be able to.

Conclusions

This prospective, investigator-blinded, randomized controlled study shows that two weeks of soak and smear is not more effective than two weeks of application of topical corticosteroid to dry skin in children for the treatment of atopic dermatitis. Instead, both arms—soak and smear and control— showed equivalent clearance rates as assessed by the objective EASI score. Both interventions displayed remarkably high clearance rates of disease. Our patients were referred to us from their pediatricians or community dermatologists and had originally failed therapy from these first-line medical providers. The undiscriminating improvement in AD clearance can most likely be attributed to the other interventions provided in this study, mainly education, which alleviated steroid phobia, a phone call after

one week, which encouraged patients to continue adhering to therapy, and homework, which reminded patients and caregivers on a daily basis to adhere to treatment.

Future Directions

This study is the first to dispute the efficacy of soak and smear, and larger studies are needed to further validate its claim. Additionally, if the results of this study are indeed true, then in *vivo* studies on the effect hydration has on the penetration of topical medications through the epidermal barrier are warranted to further assess drug penetrance through the epidermal barrier. It is also possible that soak and smear does indeed enhance skin hydration and topical drug delivery, and that the two-week endpoint selected for our study was unnecessarily long and allowed the control arm to catch up in terms of efficacy. A future study with a shorter treatment period of one week would help clarify this possibility. From asking caregivers about the quantity of topical corticosteroid they used for AD treatment at the time of initial presentation to our clinic, we suspected that most of our patients had failed topical corticosteroid from their pediatrician because they were applying inadequate amounts of topical medication. A future study quantifying the effect that quantity of topical corticosteroid has on the clearance rate of atopic dermatitis in children should also be performed.

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APPENDIX

Appendix 1: Educational Hand-out

Maintenance Treatment: Strategies to Prevent Further Outbreaks

1. Apply fragrance-free moisturizer on slightly moist skin after showering or washing hands

Repeated wetting (i.e., baths, showers, swimming) without moisturization will actually dry out the skin more. Less thick moisturizers may be used during the daytime, with petroleum jelly or petroleum jelly based moisturizers always available for more intense moisturization at night.

Recommended Moisturizers

- Cetaphil cream
- CeraVe Cream
- Aveeno for extra dry skin
- Aveeno eczema therapy
- Eucerin Cream
- Aquaphor Ointment
- Vaseline petroleum jelly
- Theraplex Emollient

Light moisturizers

Heavy moisturizers

2. Limit the use of cleansers to armpits and groin

Try to use cleansers rather than soap. Using cleansers in the shower can further dry out the skin by removing the oils the skin naturally produces. You can get clean and help your skin by limiting the use of cleansers to the armpits and groin.

Recommended Soap-free Cleansers

- Cetaphil
- Cetaphil restoraderm
- Aquanil
- Neutrogena
- CeraVe cleanser
- Unscented Dove

3. After bathing, gently pat dry

Be careful not to rub the skin, which can be thought of as scratching in disguise.

Appendix 2: Soak and Smear Instructions

Soak and Smear Patient Educational Instruction Sheet

Atopic Dermatitis (AD)

AD (or eczema) is a chronic condition of the skin that can cause itchiness and redness. Children with AD have sensitive skin, more sensitive than normal skin. Sensitive skin is more easily irritated (which causes the itchiness) by dryness and irritants in the environment (such as wool in clothing or certain detergents). AD can be controlled with good skin care and environmental measures (avoiding things that irritate your skin).

Soaking and Smearing

This is an aggressive treatment that is messy (find an old pair of pajamas) and slightly time intensive. This regimen may use a medication you have used before without success. But this medicine is being used in a different way as part of an intensive treatment regimen that must be followed exactly to work. This treatment can lead to marked improvement in even a couple of days.

The soaking will allow water to go into the skin and hydrate it, then smearing on the ointment will

1) trap water in the skin (because water cannot move through oil) and moisturize the skin

2) allow the medication to absorb into the skin better.

Usually patients do the soaking and smearing at night for 2 weeks.

The soaking and smearing treatments are done at night because the ointment on your skin will get on your pajamas instead of your clothes (that you wear during the daytime) and the ointment will be on your skin for several hours while you sleep. You may wish to use an old pair of pajamas, older sheets/blankets and even make use of a mattress pad during this treatment to protect your bed from the excessive oil.

Soak in a bath (not a shower) in plain, lukewarm water for 10 minutes (use a timer) at night, THEN immediately without drying the skin smear, , on the corticosteroid ointment. This should be done nightly for 14 days.

Throughout the treatment period you should apply the medication to the affected areas in the morning on dry skin (i.e. not using the soak and smear method)

Appendix 3: Standard Regimen Instructions

Standard Care Patient Educational Instruction Sheet

Atopic Dermatitis (AD)

AD (or eczema) is a chronic condition of the skin that can cause itchiness and redness. Children with AD have sensitive skin, more sensitive than normal skin. Sensitive skin is more easily irritated (which causes the itchiness) by dryness and irritants in the environment (such as wool in clothing or certain detergents). AD can be controlled with good skin care and environmental measures (avoiding things that irritate your skin).

The corticosteroid ointment will simultaneously

1) moisturize your skin and keep it from drying out

2) decrease the itch that you may feel, help you scratch your skin less

How to apply your medication ointment

Usually patients apply their corticosteroid ointment twice daily, once in the morning, once at night for 2 weeks. Throughout the treatment period you should apply the medication to the affected areas on dry skin. If applying after a bath or shower, wait at least 15 minutes until the skin is dry before applying the corticosteroid ointment. DO NOT apply the corticosteroid ointment to wet skin.

Appendix 4: Guardian Check Sheet

ECZEMA CHECK SHEET

WEEK 1

DAY:							
Did you do the treatment regimen?							
How did you sleep? (0-3)							
Itch level (0-10)							
Overall assessment (0-10)							

WEEK 2

DAY:							
Did you do the treatment regimen?							
How did you sleep? (0-3)							
Itch level (0-10)							
Overall assessment (0-10)