ORIGINAL RESEARCH

A Novel Hydrocortisone-Ethanol Gel Ointment for Treating Atopic Dermatitis in Children: A double blind, randomized, controlled clinical trial

Dale L Pearlman, MD[1]

[1]Orliderm Inc., Menlo Park, CA

ABSTRACT

Importance: Current treatments for moderate to severe atopic dermatitis (AD) in children are limited by incomplete efficacy, long time to benefit, and parental concerns about safety. This study evaluated a novel ointment for treating AD containing 1% hydrocortisone and 17% dispersed ethanol gel micro bubbles.

Observations: 20 children with moderate to severe AD participated in a one-week double blind, randomized, and controlled clinical trial. They were randomly assigned to apply BID either an ointment with 1% hydrocortisone ointment (HC) or a novel ointment containing 1% hydrocortisone and dispersed ethanol gel droplets (HC-EG). The primary endpoint was superiority of HC-EG over HC ointment in SCORAD score improvement during therapy. A secondary endpoint was improvement in pruritus score during therapy. Both the primary and secondary endpoints were reached in this study. SCORAD score improved 74% on average with HC-EG ointment vs 41% with HC ointment (p=.02). Pruritus score improved 68% on average with HC-EG ointment vs 37% with HC ointment (p=.009). No toxicity requiring stopping therapy was observed in either treatment group.

Conclusions and Relevance: In this small controlled study HC-EG ointment was superior to HC ointment both in improving visible rash and pruritus of AD. Parents felt HC-EG ointment was safe because it contains no prescription corticosteroids, prescription immunosuppressants, or antibiotics. Independent, larger studies would be a next step in evaluating further this new way to treat AD.

INTRODUCTION

Atopic dermatitis (AD) affects 17% of children[1] and 7% of adults in the USA[2]. Moderate to severe AD disrupts the lives of children and their families[3]. Current therapies' success is limited by low efficacy (40-60%), long duration of treatment (3-12 weeks[4,5]) and parental concerns about treatment safety. They worry antibiotics may cause antibiotic resistant bacteria[6]. More than 50% of patients (or their caregivers) turn to alternative (complementary) therapies because of these concerns[7].

A key component of AD therapy is directed at suppressing bacteria. Staphylococcus aureus is a primary trigger of the inflammatory changes in AD. Patients with atopic dermatitis are colonized by extremely high levels of Staphylococcus aureus[8]. The patients have elevated levels of IgE directed

against staphylococcal cell surface proteins[9]. Oral antibiotics, topical antibiotics, and bleach baths are often used to treat AD[10].

A novel antibacterial strategy could be topical application of alcohol-based hand sanitizer gel (ABHSG). Such gels contain 62-70% ethanol and are reported to be 99.999% effective against staphylococci[11]. Children under the age of six years old may use ABHSG's if an adult supervises the application[12]. One cannot directly apply ABHSG to eczematous skin because of stinging.

While there is evidence that ethanol in solution with hydrocortisone does enhance delivery of the hydrocortisone across the skin[13], we could find no report in the literature when the ethanol is in the form of gel microbubbles dispersed in an ointment. To use ABSHG in topical therapy of AD we needed to develop a new topical formulation which would prevent stinging, block possible absorption of ethanol and hydrocortisone across eczematous skin, and avoid exacerbating skin dryness. The novel ointment contains the ethanol in the form of dispersed ABHSG microbubbles. The dispersion minimizes stinging and absorption. Skin dryness is avoided by using an ointment vehicle and because ABHSG contains moisturizers.

METHODS

Trial design

This is a double blind, randomized, controlled trial design in which neither the Principle Investigator (PI), patients, nor parents know whether HC or HC-EG ointment is used. Patients are randomly assigned to a treatment group. Patients have a pre-therapy visit and an end-therapy visit. At each visit the PI determines a modified SCORAD score based on surface area affected and the degree of redness, scaling, oozing/crusting, swelling, and excoriations. At each visit the parents score the pruritus in the preceding 24 hours on a 0 to 10 point scale. At the end-therapy visit parents are asked about local stinging with treatment, any change in skin color (blanching) where the ointment is applied, and signs of ethanol intoxication.

Participants

Written informed consent to participate and for photographs was obtained from the parents of the children participating. All photographs maintain the anonymity of the participant. No compensation was paid for participation.

An independent IRB function was provided by a group of pediatricians at a local multispecialty clinic. They reviewed and approved the study design. The principles outlined in the Declaration of Helsinki were followed.

Criteria for entry:

1) At the initial visit crusted and oozing lesions on some or all of these areas: trunk, limbs, and face.
2) History of inadequate response to prior used over-the counter ointments as well as to one or more of the following prescription medications: topical corticosteroids, topical calcineurin inhibitors, and topical and oral antibiotics.
3) Age 3 months and older.

Intervention

The test ointments were pre-formulated for dispensing.

a) HC ointment: Aquaphor® and corticosteroid 2.5% ointment in a ratio to yield 1% concentration of hydrocortisone.

b) HC-EG ointment: Aquaphor®, corticosteroid 2.5% ointment, and 70%

ethanol gel in a ratio to yield 1% hydrocortisone and 17% by volume ethanol gel.

Treatment

Patients applied at home a saturating dose of the assigned ointment to the affected areas BID for a week. A "saturating dose" meant apply ointment until no more will absorb and then wipe off the excess with a paper towel.

During the clinical trial the only allowed topical treatment was the assigned ointment. The only oral therapy allowed was prn use of prior used oral antihistamines.

Outcomes

The primary endpoint was superiority in average SCORAD improvement in patients treated with HC-EG ointment vs HC ointment.

Secondary endpoints were:

1. Pruritus: superiority of HC-EG ointment vs HC ointment in average reduction in pruritus score.
2. Enhanced corticosteroid absorption: lack of difference in skin blanching between the two treatment groups.
3. Adverse effects local: stinging at time of application
4. Adverse effects systemic: symptoms of ethanol intoxication: lack of difference in symptoms of mental confusion, slurred speech, and difficulty walking between the two groups.
5. Parental concern about the safety of the medication.

RESULTS

Recruitment

20 patients were recruited from the local pediatricians who had reviewed and approved the study protocol. All 20 patients were available at the initial and end therapy visit. Age ranged from 3 months to 12 years.

Primary endpoint:

Average SCORAD improved 74% in the HC-EG ointment treated patients vs 41% in the HC ointment treated patients. This is a statistically significant difference with p=.02 (Table 1).

These data are especially interesting in that they demonstrate that HC-EG ointment is better at treating more severe cases than HC ointment is at treating milder cases. By random assignment in this study, the patients

Table 1: Change in SCORAD score in 20 patients with moderate to severe atopic dermatitis randomly assigned to apply for one week twice daily either 1% hydrocortisone (HC) ointment or 1% hydrocortisone ointment-ethanol gel (HC-EG).

Average SCORAD score	10 Patients using HC ointment	10 Patients using HC-EG ointment
Pre-Treatment	28.9	42.1
End-Treatment	17.1	10.9
Average change Pre to End Treatment	-40.8%*	-74.2%*

*Statistically significant different between HC and HC-EG ointment group p=0.02.

Table 2: Change in pruritus score in 20 patients with moderate to severe atopic dermatitis randomly assigned to apply either for one week twice daily 1% hydrocortisone (HC) ointment or 1% hydrocortisone ointment-ethanol gel (HC-EG) ointment.

Average Pruritus Score (0-10)	10 patients used HC ointment twice daily	10 patients used HC-EG ointment twice daily
Pre-treatment	6.1	6.1
End-treatment	4.1	1.95
% improvement	37%*	68%*

*Statistically significant different between HC and HC-EG ointment group p=0.009.

that used HC-EG ointment turned out to be a more severe group than the group who received HC ointment. At entry into the study the patients assigned to HC-EG ointment had a worse average SCORE than the HC ointment group (42.1 vs 28.9). Despite starting with a worse average SCORAD at entry, the HC-EG ointment cohort ended treatment with a better average SCORAD score at the end of therapy (SCORAD of 10.9 with HC-ED ointment vs 17.1 with HC ointment)

For examples of the degree of improvement with the HC-EG vs HC ointment see Figure 1 and Figure 2.

Secondary endpoints:

Pruritus: Average score was 68% improved in the HC-EG ointment treated patients vs 37% in the HC ointment treated patients. This is a statistically significant difference with p=0.009 (Table 2).

Stinging: One of ten of the HC-EG ointment treated patients experienced mild to moderate stinging when the ointment was applied. The remaining 9 patients and all the HC ointment patients reported no stinging. The stinging was relieved and the patient continued treatment by first applying a layer of Aquaphor® and then the ointment for the first two days of therapy. After day two of therapy no further pre-application of Aquaphor was needed.

Local corticosteroid effects via percutaneous absorption on eczematous skin: No patient in either cohort exhibited local blanching at the post-therapy examination or parent reported seeing blanching during treatment at home.

Evidence of systemic ethanol effect via percutaneous absorption on eczematous skin: None of the treated patients in the study

Figure 1: A patient with atopic dermatitis behind the knee randomized to treatment with HC ointment. A) Before treatment. B) After 1 week of HC ointment.

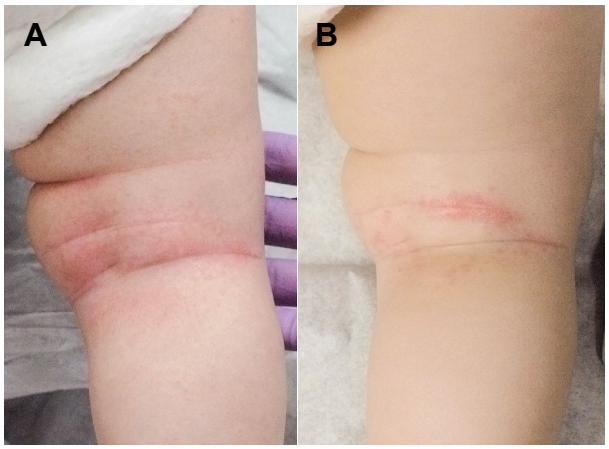
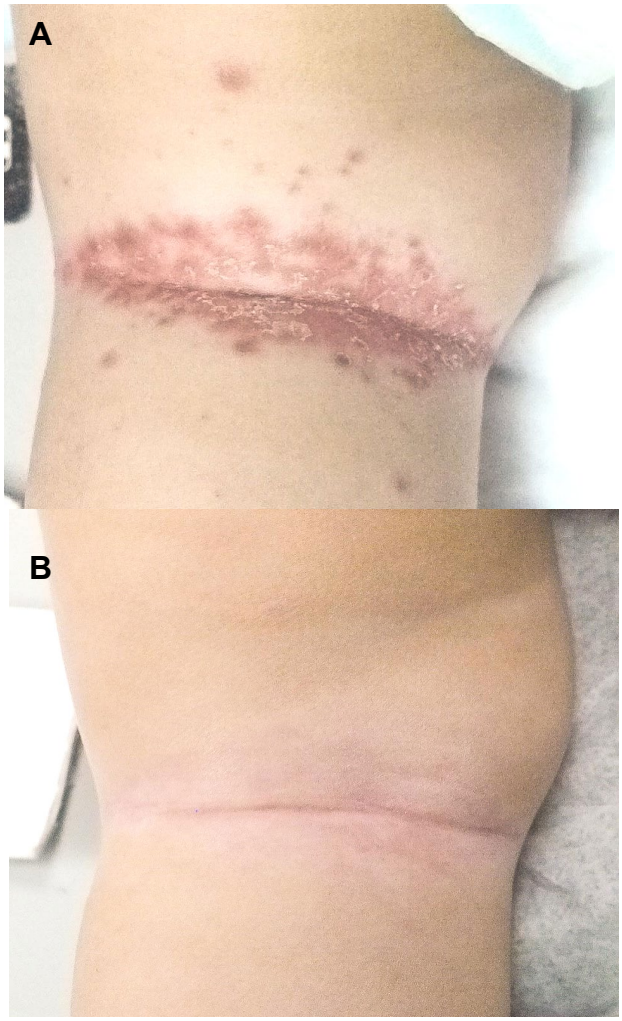


Figure 2: Another patient with more severe atopic dermatitis behind the knee randomized to treatment with HC-EG ointment. A) Before treatment. B) After 1 week of 1% HC-EG therapy.



evidenced at end-therapy exam or was reported by parents during home therapy to have mental confusion, impaired balance, unsteady walking, or other signs of inebriation.

Concerns of patients about the safety of the study medications: All said they felt safe and comfortable about the ingredients in the study ointments and using them as directed to treat the AD.

DISCUSSION

Limitations of this study include the small sample size and the potential bias by the Principle Investigator due to conflict of interest.

In this study we hypothesized that the dispersed ethanol gel microbubbles in the hydrocortisone ointment would increase efficacy by suppressing the eczematous skin's staphylococcal population. While this study showed the anticipated increased clinical efficacy, the antibacterial basis for the improvement was not investigated in this trial. We did not measure the change in the staphylococcal biofilm population before and after treatment. Thus further study will be needed to assess evaluate this hypothesized mechanism of action.

In these patients with moderate to severe AD, 1% hydrocortisone-ethanol gel (HC-EG) ointment was superior to 1% hydrocortisone ointment (HC) in both objective improvement and reduction in pruritus. Local irritation was minimal and easily managed. No systemic signs of ethanol intoxication occurred. Parents reported their preference for HC-EG because of its rapid efficacy and being free of prescription corticosteroids and antibiotics. This is significant as parental noncompliance due to safety concerns can interfere with treatment.[14,15]

Conflict of Interest Disclosures: The principle investigator and article author is the inventor and holds patents on this new technology.

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Corresponding Author:
Dale L. Pearlman, MD
Orliderm Inc.
Menlo Park, CA
md@dpearlman.biz

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