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MINIREVIEWS

New innovation of moisturizers containing non-steroidal anti-inflammatory agents for atopic dermatitis

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Abstract

Atopic dermatitis is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children. The standard management consists of a combination of anti-inflammatory drugs in adjunctive with skin care management particular moisturizer application. A concern for the side effects associated with long term use of corticosteroids has also been considered. There has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, mineral and lipids. The *in vitro* and the *in vivo* studies of each agent were reviewed. The clinical study on the efficacy of moisturizers containing these agents were also demonstrated including the author's studies and clinical experience. These moisturizers might be considered as an alternative treatment in acute flare of mild to moderate atopic dermatitis.

Key words: Non-steroidal anti-inflammatory agents; Moisturizer; Atopic dermatitis

Core tip: The skin care management particular moisturizers play an important role in atopic dermatitis. The side effects of corticosteroids are limited in their use in this disease. Take together, a new moisturizer containing various anti-inflammatory substances have been developed to be used as an alternative treatment to avoid the side effects of corticosteroids. These agents are divided into herbal extracts, vitamins, minerals and lipids. The clinical trials on the effectiveness of these moisturizers were reviewed. The author's clinical experience also discussed.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children and influences the quality of life.

The etiology of AD seems to result from a combination of barrier dysfunction, immunodys function, genetics, autoimmunity, *Staphylococcus aureus* and environmental factors[1].

The standard management of AD consists of a combination of anti-inflammatory drugs in adjunction

Table 1 Type of anti-inflammatory agents

Herbal extracts
Licorice
Glycyrrhiza inflate (Licochalcone A)
Glycyrrhiza glabra (Glycyrrhetinic acid)
Chamomile
Matricaria recutita (Bisabolol, chamazalene, apigenin)
Vitamins and minerals
Provitamin B5 (Dexpanthenol)
Vitamin B3 (Niacinamide)
Zinc
Lipids
Natural sources of lipids
N-palmitoylethanolamide extracted from palm oil
Linoleic acid extracted from:
Shea butter (*Butyrospermum parkii*)
Canola oil
Argar oil
Kernel oil
Spent grain wax
Portulaca oleracea Linn
Phytosterol extracted from shea butter
Synthetic lipids
Ceramides
Pseudoceramides

with skin moisturization and avoidance of triggering factors. A concern for the side effects associated with long term use of corticosteroids has also been considered.

For the past five years, there has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, minerals and lipids. The anti-inflammatory property of these agents are demonstrated in *in vitro*, *in vivo* studies, as well as the clinical trials on the patients with AD, psoriasis and seborrheic dermatitis.

From the literature reviews of clinical researches on these moisturizers, they are divided into 3 groups according to the active ingredients of anti-inflammatory agents as follows: herbal extracts, vitamins, minerals and lipids (Table 1). The evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents are summarized in Table 2.

HERBAL EXTRACTS

There are two active ingredients extracted from two species of Licorice: (1) Licochalcone A (LA), extracted from *Glycyrrhiza inflate*; and (2) Glycyrrhetinic acid, extracted from *Glycyrrhiza glabra*.

There is an *in vitro* study that demonstrates that LA, a major phenolic component of *Glycyrrhiza inflate*, has anti-inflammatory as well as antimicrobial effects[2,3]. It could inhibit cytokines production from T cells and monocytes as well[2-4]. The study shows that LA could reduce shave-and ultraviolet (UV)-induced redness[4]. Moreover, the improvement of the rosacea patients is also reported in a clinical study in which skin care product containing LA was applied for 8 wk[5].

In 2010, Udompataikul *et al*[6], conducted a comparative trial of moisturizer containing LA and linoleic acid *vs* 1% hydrocortisone (HC) for the treatment of childhood AD. It was a randomized controlled-investigator blind study. LA lotion were applied on one side of the patients' body and HC lotion on the opposite side, twice daily for 6 wk. The clinical outcome was assessed using the scoring of AD (SCORAD) score. The relapse rate was recorded and analysed using survival analysis. Thirty patients were enrolled, 26 patients completed the protocol. The mean age was 5.8 years old. The average baseline SCORAD score was 28 on both sides (moderate severity). The response rate of both agents was 73.33%. There was no statistical significant group difference in the reduction of SCORAD score. Though the edema and erythema score in HC treated area had more rapid improvement than that of LA treated side, there was no significant difference. The relapse rate of HC-treated side was higher than that of LA-treated side. However, there was no significant difference. No side effect was observed from both agents. It was concluded that the effectiveness of moisturizer containing LA was equal to that of HC lotion. It could be used as an alternative treatment for both acute flare and in maintainance phase of mild to moderate childhood AD.

There was also a multicenter, randomized,split-side double blind study in 55 children between the age of 3 mo to 14 years with mild to moderate AD. It was shown that LA had a similar result in terms of improved SCORAD and reduces transepidermal water loss (TEWL) compared with 1% HC[7].

In 2014, Angelova-Fischer *et al*[8], designed a comparative study of moisturizer consisted of LA, linoleic acid, decanediol and menthoxypropanediol (LALDM) *vs* 1% HC for mild to moderate AD treatment. Twenty patients were included. The mean age was 26.2 years old (16-65 years old). It was discovered that LALDM and 1% HC can reduce SCORAD scores, pruritus, erythema, TEWL and increase in skin conductance without statistically significant difference between two groups. Moreover, LALDM can reduce *Staphylococcus aureus* colonization with statistically significant difference from 1% HC. Decanediol has antibacterial activity. Menthoxypropanediol, a synthetic derivative of menthol can improve the pruritic symptom by triggering cold-sensitive receptors in the skin which is responsible for cooling sensation.

Glycyrrhetinic acid also possesses anti-inflammatory property[9]. Abramovits *et al*[10], conducted a randomized, vehicle-controlled clinical trial to examine the effectiveness of MASO63DP cream, which composed of shea butter and Glycyrrheticnic acid, in the management of mild to moderate AD. 218 patients, age between 18-84 years old, were included in this 50-d study. The clinical outcomes were assessed using Eczema Area and Severity Index score and Investigator's Global Assessment. It was found that the incidence of rash

Table 2 Evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents

Ref.	Active ingredients	Design + Population + Age	Outcome measurement	Results
Udompataikul *et al*[6]	Licochalcone A, LA	Randomized controlled-investigator blind; *n* = 28, mean age = 5.8 yr old (2-15 yr old)	SCORAD score	Response rate 73.33% The effectiveness of LA was equal to 1% HC
Wananukul *et al*[7]	Licochalcone A, LA	Randomized, double-blind, split-side, study *n* = 55, age 3 mo-14 yr old	SCORAD score, TEWL	The effectiveness of LA was equal to 1% HC
Angelova Fischer *et al*[8]	LALDM	Randomized controlled-investigator blind, study; *n* = 20 mean age = 26.2 yr old	SCORAD score, TEWL, skin -conductance, *Staphylococcus aureus* colonization	LALDM was equal to 1% HC, and LALDM can reduce *Staphylococcus aureus* colonization
Abramovits *et al*[10]	Glycyrrhetinic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; *n* = 218, age 18-84 years old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Boguniewicz *et al*[11]	Glycyrrhetinic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; *n* = 142, age 18-84 yr old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Udompataikul *et al*[20]	Dexpanthenol, petrolatum	Open label; *n* = 30 mean age 7.19 yr old	SCORAD score	The effectiveness of dexpanthenol ointment was equal to 1% HC
Eberlein *et al*[30]	PEA, phytosterol ceramide in dermal membrane structure	Multicenter study (moisturizers as adjuvant treatment) *n* = 2456 (adult 1533, children 923)	Clinical and pruritic VAS	Pruritus reduction (VAS), Improvement of sleep quality, Reduction of previous use of topical corticosteroid were significant difference
Udompataikul *et al*[20]	Linoleic acids from Spent grain wax, shea butter, argan oil; phytosterols (LP)	Randomized investigator blind; *n* = 31, age = 4.24 yr old	SCORAD score	The effectiveness of LP was equal to 1% HC
Lee *et al*[40]	Multilamellar emulsion – pseudoceramide, type III synthetic ceramide (PC)	An open crossover study	Clinical	PC cream was more effective than urea cream

LA: Linoleic acid; SCORAD: Score of Atopic Dermatitis; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; TEWL: Transepidermal Water Loss; VAS: Visual Analogue Scale; LALDM: Licochalcone A, linoleic acid, decanediol menthoxypropanediol; PEA: N-palmitoyl ethanolamine.

was 2.1% in MASO63DP group *vs* 5.5% in the vehicle group. MASO63DP was statistically more effective than vehicle. Two patients discontinued using MASO63DP because of an adverse effect[10]. Boguniewicz *et al*[11], also conducted the same clinical study in 142 childhood AD patients. It was concluded that MASO63DP is an effective monotherapy for mild to moderate AD in infant and children[11].

Chamazulene (terpenoids) is a major active ingredients extracted from chamomile (*Matricaria recutita*). It possesses anti-inflammatory property by inhibiting histamine release from mast cells and leukotriene B4 from white blood cells[12,13]. In addition, Apigenin, flavonoids agents found in chamomile also has anti-inflammatory and antioxidant effect[14]. It was discovered that these active agents decrease UV induced erythema[15]. Chamomile is commonly used as an active ingredient in combination with Zinc or dexpanthenol (DT) in protective cream for irritant contact diaper dermatitis.

VITAMINS AND MINERALS

DT, an alcoholic analog of pantothenic acid, as water-in-oil emulsion, is rapidly penetrated through the skin[16]. Pantothenic acid is essential for normal epithelial function and is a component of coenzyme A, a cofactor for catalytic enzyme in carbohydrate, fatty acid, protein, sterol and porphyria metabolism[17], 2%-5% of DT acts like a humectant moisturizer[17-19]. It was shown that DT has anti-inflammatory action on UV-induced erythema and irritation model[17]. Furthermore, DT plays an important role in wound healing by activation of fibroblast proliferative and acceleration of re-epithelization. The ointment consisted of 2%-5% DT is effective for the treatment of burns, anal fissures, leg ulcers, diaper dermatitis, and sodium lauryl sulfate induced irritant contact hand dermatitis in AD patients[17]. The comparative study of 5% DT in w/o emulsion *vs* 1% HC ointment in the treatment of mild to moderate childhood AD was also investigated[20]. Thirty patients with mean age of 7.19 years old enrolled.

Twenty-six patients completed the study. The results exhibited that the efficacy of DT and HC to reduce SCORAD scores were not significantly different at the end of the study (week 8). However, HC could relieve edema faster than DT with a significant difference (within week 1 *vs* week 2 respectively). Hence, this study also demonstrates that DT has a beneficial role as an alternative treatment in mild to

moderate severity of childhood AD.

Niacinamide (vitamin B3) demonstrates anti-inflammatory action by inhibiting the histamine release from mast cells[21]. It also increases ceramides biosynthesis and other stratum corneum lipids to improve the epidermal barrier function[22]. Zinc exhibits the anti-inflammatory response by blocking cytokine release from monocytes[23]. It is commonly used in the barrier cream for the treatment and prevention of irritant contact diaper dermatitis.

LIPIDS

Lipids with the occlusive effect, help prevent TEWL from the skin. As a result, it keeps the skin moist. The types of lipids which possess anti-inflammatory properties are as follows.

Natural sources of lipids

N-palmitoylethanolamine: N-palmitoylethanolamine (PEA), a fatty acid derivative that belongs to the family of N-acylethanolamines. PEA used in commercial moisturizers, is extracted from palm oil. It is physiologically produced by keratinocyte and is found in the stratum granulosum of human skin. The major roles of PEA are to be used as an anti-inflammatory, antioxidant and analgesic compound. The mechanism of action is *via* cannabinomimetic action on cannabinoid receptors (CBR) located on mast cells and cutaneous nerve fibers[24,25]. CBR agonists significantly decrease histamine induced pruritus and vasodilatation after they are topically applied on the skin[26]. An anti-inflammatory action of PEA was clinically demonstrated. PEA was incoperated into a lamellar matrix cream which was used in these studies. It was shown that this cream could alleviate the irritative facial skin lesions[27] and uremic pruritus[28]. Moreover, HC cream and this cream were equally effective in 18 patients with mild to moderate AD[29]. A recent 6-wk multicenter trial study illustrated that intensities of erythema, pruritus, excoriation, scaling, lichenification and dryness were significantly reduced with a combined score of 58.6% among the whole group of patients according to the doctors' reports. A pruritus reduction on visual analogue scales from 6 d through 6 wk of treatment with significant difference from baseline was reported, and the patients' sleep quality was significantly improved as well. Previous use of topical corticosteroids were significantly reduced by 56% while the average weekly application rate decreased by 62%. Therefore, this cream demonstrates a benefit in the AD management[30].

ESSENTIAL FATTY ACIDS AND STEROLS

Essential fatty acids like Omega 3, Omega 6 and sterols as phytosterols possess an anti-inflammatory property. They help reduce the production of prostaglandins. They are found in the seeds of many plants, including shea butter, spent grain wax, argan oil, kernel oil, canola oil[31], as well as in the roots, leaves and stems of purslane *(Portulaca oleracea* Linn)[32,33].

Recently, the study of moisturizing cream consisted of linoleic acids from spent grain wax, shea butter, argan oil and phytosterols from shea butter has been conducted in 31 patients with mild to moderate AD. The mean age was 4.24 years old. It was also shown that this cream is equally effective to HC. Thus, it is considered as an alternative monotherapy for childhood AD with mild to moderate severity[34].

Synthetic lipids

Natural stratum corneum ceramides structurally consist of a polar amide group and non-polar alkyl chains. They are capable of assembling to form the lamellae[35]. However, since the natural ceramides are extremely expensive and difficult to formulate, the new pseudoceramides, for example 1,3-bis-(N-(2-hydroxyethyl)-palmitoylamino)-2-hydroxypropane, have been developed[35]. Pseudoceramides have similar molecular properties to ceramides. The synthetic ceramides have been developed as well.

Park *et al*[36], discovers that the molecular organization of multilamellar emulsion-pseudoceramide and type Ⅲ synthetic ceramide as characterized as the lateral hexagonal phase are similar to the human stratum corneum intercellular lipid. Moreover, synthetic ceramides show anti-inflammatory effect both in *in vitro* and *in vivo*, and prove to be beneficial in an animal model of AD[37-39].

There was a clinical comparative study on anti-inflammatory property of multilamellar emulsion containing pseudoceramide and synthetic ceramide (ME) *vs* urea cream. It concluded that ME cream was more effective than that of urea in mild to moderate childhood AD[40].

AUTHOR'S CLINICAL EXPERIENCE AND COMMENTS

From author's clinical practice experience, corticosteroids, calcineurin inhibitors and moisturizer skin care are standard treatment for AD patients. Nevertheless the moisturizers containing anti-inflammatory agents can be used as an alternative treatment instead of corticosteroids or calcineurin inhibitors in mild to moderate severity of AD patients, and in the maintenance phase as well. They are particularly suitable for some selected cases whose parents are corticosteroid phobia. However, the anti-inflammatory responses especially, the edema and erythema parameter might be slower than corticosteroids. This information should be informed to the patients. In these particular cases, when these moisturizer that contained anti-inflammatory agents were used to treat as an alternative first line of treatment for a couple of weeks with slow response rate, the

corticosteroids should be added on. It was found that these moisturizers could reduce the frequency of corticosteroids use in the treatment.

CONCLUSION

Because particular skin care moisturizers play an important role in AD management, the side effects of an anti-inflammatory agents like corticosteroids are limited in their use in AD. Taken together, new moisturizers containing various substances have been developed to be used as monotherapy in mild to moderate AD. These agents are herbal extracts, vitamins and minerals and lipids. They can be used as an alternative treatment and in the maintenance phase of AD. The further researches for new anti-inflammatory substance should be conducted.

However, the long term side effect of the treatment with these moisturizers should be warranted, and the pricing of these moisturizers should also take into consideration.

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