Efficacy and Safety of Topical Urea for Treatment Atopic Dermatitis as a Reference in the National Drugs Formulary

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Abstract

Atopic dermatitis (AD) is a chronically relapsing skin disease that occurs most commonly during early infancy and childhood. One of the most important clinical features of AD which results from a dysfunctional epidermal barrier (EB) is very dry skin (xerosis). Moisturizers are often used as supplements to topical and/or systemic anti-inflammatory drugs in various types of skin conditions and disorders. Humectan, this class of moisturizer is used to improve the appearance and texture of skin by filling in the crevices between corneocytes. One of the humectant included in the list of the National Drugs Formulary that is needed and must be available at health service facilities as a reference in the implementation of National Health Insurance (NHI) is urea. The literature searches using Pubmed, Academia, Google scholar and published in the last 10 years. Urea is effectively increasing skin hydration as well as niacinamide, significantly reducing local Scoring Atopic Dermatitis (SCORAD) and stratum corneum (SC) hydration. Urea had a decrease in transepidermal water loss (TEWL) which was not significantly better than lanolin and ceramide. The ceramide had a lower mean Visual Analogue Scale (VAS) score for irritation compared with the urea. More participants also preferred the ceramide-based cream over the urea. Urea is an effective and safe treatment although not as well as ceramide. Ceramide has been shown to be more effective and less irritating than urea. Ceramid can be quite expensive, while urea is a moisturizer that is easily found and accessible to the public.

Keywords: Atopic Dermatitis, Moisturizer, Humectan, Topical Urea

1. Introduction

Atopic dermatitis (AD) is a chronically relapsing skin disease that occurs most commonly during early infancy and childhood (Goldsmith et al., 2012). Atopic eczema (atopic dermatitis) is characterized by an itchy red rash that favors the skin creases, such as the folds of the elbows, behind the knees, and around the neck (Williams et al., 2014).

AD is a major public health problem worldwide, with a prevalence in children of 10–20% in the United States, Northern and Western Europe, urban Africa, Japan, Australia, and other industrialized countries. The prevalence of AD in adults is approximately 1–3%. Interestingly, the prevalence of AD is much lower in agricultural regions of countries such as China and in Eastern Europe, rural Africa, and Central Asia (Goldsmith et al., 2012).

In Southeast Asia, the prevalence of AD varies between countries from 1.1% in 13-14 years old at Indonesia to 17.9% in 12 years old at Singapore. Incidence tends to increase 2-3 times in the last decade. Based on data from the Allergy Immunology Division of the Outpatient Unit (OU) of Dermatology and Venereology, Dr.

Soetomo, the prevalence of AD patients in 2009-2011 was 353 patients (Ratnaningtyas and Hutomo, 2019).

One of the most important clinical features of AD which results from a dysfunctional epidermal barrier (EB) is very dry skin (xerosis) (Nasrollahi et al., 2018). Moisturizers are often used as supplements to topical and/or systemic anti-inflammatory drugs in various types of skin conditions and disorders, such as contact dermatitis, atopic dermatitis, psoriasis, and ichthyosis, in order to bring relief and break a dry skin cycle (Lodén and Maibach, 2012). Moisturizers with different agents containing varying amounts of emollients, occlusives, and/or humectants are used to reduce transepidermal water loss (TEWL), increase skin hydration, and thus improve xerosis in AD patients (Nasrollahi et al., 2018). Humectan, this class of moisturizer is used to improve the appearance and texture of skin by filling in the crevices between corneocytes (Nolan and Marmur, 2012).

Humectants, such as lactic acid, urea and pyrrolidone carboxylic acid, and preservatives, like benzoic acid and sorbic acid, are known to be able to cause such subjective sensations (Lodén, 2016). Some patients reported disagreeable skin sensations from urea treatments, such as redness, stinging and smarting (Ho et al., 2020).

One of the humectant included in the list of the National Drugs Formulary that is needed and must be available at health service facilities as a reference in the implementation of National Health Insurance (NHI) is Urea. Urea available in 10% and 20% cream preparations at Healthcare facilities level 1, 2, and 3.

This study reviews the efficacy and safety of urea in the National Drugs Formulary as a reference of the implementation of NHI.

2. Methodology

The literature searches using Pubmed, Academia, Google scholar were performed using key words including “atopic dermatitis”, “moisturizer”, and “urea”. No language of publication restriction was set for the literature search. The literature search was published in the last 10 years, and carried out by one reviewer dependently. The research question and literature search strategy were based on the PICOS (population; intervention; comparator; outcomes; study type) framework. The following eligibility criteria were selected:

- Population: patients of any age who underwent atopic dermatitis;
- Intervention: urea topical with any formulation;
- Comparator: another moisturizer with any type and formulation;
- Outcome: increasing skin hydration, decreasing TEWL, decreasing Scoring Atopic Dermatitis (SCORAD)
- Study design: only systematic reviews or meta-analyses of primary studies on human subjects were considered eligible for this review.

3. Result

Table 1. Summay of clinical studies of urea in AD

Author, Year, Country	Population	Intervention	Comparator	Outcome
Hayati et al., 2015 Indonesia	66 patients with AD	10% urea cream	4% niacinamide cream	1. Urea cream is effective increasing skin hydration of AD patients. 2. Niacinamide cream is also effective increasing skin hydration of AD patients. 3. The cure rate for skin hydration in the urea group was 93.9% and in the niacinamide group was 84.8%. 4. The results of the comparative analysis of effectiveness in both groups of urea and niacinamide were found to be not significant with p value = 0.315
Nasrollahi et al., 2018 Iran	20 patients with AD	5% urea-containing water-in-oil emulsion	1.5% linoleic acid-containing water-in-oil emulsion	1. Four weeks of treatment with a LA-containing product resulted in a significant decrease in local SCORAD, TEWL, and an increase in SC hydration compared to baseline. 2. Treatment with a urea-containing product cream resulted in a significant decrease in local SCORAD and an increase in SC hydration. TEWL reduction after application of the urea-containing product, however, was not significant.
Tabri et al., 2018 Indonesia	16 patients of AD aged 2-14 years old	10% urea cream	1% ceramide cream, 10% lanolin cream	1. From day 0 to day 7 significant decrease in TEWL value was observed in ceramide compared to control group (vaselin), while the results of urea and lanolin group were not statistically different from control. 2. From day 7 to day 14 a significant decrease in TEWL was noted in ceramide group compared to control group (vaselin), while the results of urea and lanolin group were not statistically different from control. 3. On day 14, there were no patients with abnormal skin barrier in the 1% ceramide group.
Ho et al., 2020 Singapore	42 participants of patients aged between 8 and 16 years diagnosed with AD	5% urea cream	ceramide-based moisturizer	1. The ceramide-based cream had a lower mean VAS score for irritation compared with the urea 5% cream. 2. More participants also preferred the ceramide-based cream over the urea 5% cream as their daily moisturizer.

Note:
AD: Atopic Dermatitis
SC: Strarum corneum
LA: Linoleic Acid
SCORAD: Scoring Atopic Dermatitis
TEWL: Transepidermal water loss
VAS: Visual Analogue Scale

From the table, in the study of Hayati et al, there is no comparison of the effectiveness of increasing skin hydration between 10% urea cream and 4% niacinamide cream, although cure rate for skin hydration in the urea group slightly better. In the study of Nasrollahi et al, the use of 1.5% linoleic acid-containing water-in-oil emulsion was as effective as 5% urea-containing water-in-oil emulsion in reducing local SCORAD and increasing SC hydration, but urea was not effective in reducing TEWL significantly compared to linoleic acid. In the study of Tabri et al, the use of 1% ceramide cream showed the most significant reduction in TEWL than 10% urea cream and 10% lanolin cream during 14 days. In Ho et al's study, ceramide-based moisturizer was superior because they were less irritant than 5% urea cream.

3. Discussion

We included 4 studies with a total of 144 participants in this review. Urea concentration in this studies from 5% to 10% on cream and water-in-oil-emulsion. Two studies compared urea with ceramide. Each study compared urea with niacinamide, linoleic acid, and lanolin. Two studies compared increases in skin hydration, one study compared decreases in SCORAD, two studies compared decreases in TEWL, and one study compared low mean VAS scores and side effects. Due to differences in outcome measures and study designs, a quantitative meta-analytic synthesis of the results was not deemed possible. However, an overwhelming majority of the included studies verify that moisturizers have beneficial effects on skin hydration and TEWL in the studied patient population.

In the study of Nasrollahi et al, 1.5% linoleic acid-containing water-in-oil emulsion and 5% urea-containing water-in-oil emulsion significantly reduced local SCORAD for 4 weeks in patients with mild-to-moderate AD. This is supported by the study of Bissonnette et al who found a decrease in the SCORAD index of patients with atopic dermatitis using 5% urea moisturizer and 10% urea lotion (Bissonnette et al., 2010). Although this study did not discuss the effect of ceramide on SCORAD, the use of ceramid-dominant therapeutic moisturizer showed general improvement in AD (Koh et al., 2017).

Moisturizers are able to modify the skin barrier function, detected as changes in TEWL, skin capacitance, and susceptibility to an irritant, and also to change the mRNA expression of certain genes involved in the assembly, differentiation, and desquamation of the stratum corneum, as well as lipid metabolism (Lodén and Maibach, 2012).

As found in the study of Hayati and Nasrollahi et al, urea was shown to be effective in increasing skin hydration in patients with mild-to-moderate AD within 4 weeks. These results are not much different from the effectiveness of 4% niacinamide cream (Hayati et al., 2015), and 1.5% linoleic acid-containing water-in-oil emulsion (Nasrollahi et al., 2018). However, with a concentration of 5% urea also managed to show its benefits in increasing skin hydration.

The study of Nasrollahi and Tabri et al showed that urea was able to reduce TEWL in patients with mild-to-moderate AD within 2 weeks, this result was better than with 10% lanolin cream which took more than 14 days, but not as good as 1.5% linoleic acid or 1% ceramide cream. The most significant decrease in TEWL was shown at 1% ceramide concentration where no patients with abnormal skin barrier on day 14 (Tabri, F; Yuniati,

2018).

Urea is a hygroscopic molecule (capable of absorbing water), present in the epidermis as a component of the natural moisturizing factor (NMF) and is essential for the adequate hydration and integrity of the stratum corneum. A reduction in the hygroscopic capacity of the skin can increase TEWL, deregulate epidermal proliferation and inhibit skin desquamation, inducing hyperkeratosis and pruritus. Urea can increase the amount of free water in conditions of high humidity and act as a potent skin humidifier and descaling agent. Interestingly, all these clinical studies used topical formulations, either as cream, emulsion, or foam, with urea concentrations of 10% or less (Celleno, 2018).

In the study of Nasrollahi et al, patients were more satisfied using the LA-containing w/o emulsion compared to the urea-containing product. This may be explained by the stinging and burning sensation of urea immediately after its application. This is in line with Ho et al, where ceramide-based cream had a lower mean VAS score for irritation compared with the urea 5% cream with symptoms of stinging, burning, or pain. Our results suggest that this ceramide-based cream causes less irritation than the urea 5% cream in AD children with subacute or acute flares, especially in the presence of skin excoriations (Ho et al., 2020).

Numerous studies demonstrated the efficacy of 5%-12% urea cream formulations in the treatment of xerosis in atopic dermatitis. At these low concentrations tolerability is very good and no adverse reaction or mild burning/ pruritus have been reported (Annunziata et al., 2020). In 1943, Rattner patch tested 500 hospital patients, 66 of whom had skin disease, with a 3% urea cream and found no adverse reaction. Clinical and patient assessments of the use of creams with 10% urea or lower showed no evidence of inflammation and barrier damage, although occlusive exposure to 20% urea in petrolatum for 24 h causes significant inflammation (i.e. increase in blood flow and skin thickness) and increases TEWL (Lodén and Maibach, 2012).

Despite these studies, some patients reported disagreeable skin sensations from urea treatments, such as redness, stinging and smarting. Application of urea to freshly excoriated areas and to skin lesions can give burning sensations. This is not irritation in the ordinary sense and usually does not cause clinically noticeable damages to the skin, but the disagreeable sensations will reduce compliance, especially in children. (Lodén and Maibach, 2012). Urea-containing creams, when used on AD patients, have been reported to produce stinging and burning sensations, itch, and even excoriations in some series, especially when used as a 10% preparation, with more acidic-based preparations or in combination with topical 1% hydrocortisone (Ho et al., 2020).

The costs for the maintenance treatment with the 5% urea cream have also been evaluated using a Markov simulation model. The results showed the maintenance treatment to be a cost-effective option compared with no treatment in eczema free periods in adult patients with atopic dermatitis in the four Nordic countries (Lodén and Maibach, 2012).

It was subsequently concluded that an insufficiency of ceramides in the stratum corneum is an important factor in atopic dry skin. Subsequently, ceramides have been added to many moisturizes used in the treatment of both atopic and normal skin. Because ceramides are oil soluble, they can easily be incorporated into moisturizers however, many products with ceramides, especially prescription formulations, can be prohibitively expensive. (Nolan and Marmur, 2012). Other commonly used occlusive ingredients include paraffin, squalene, dimethicone, soybean oil, grapeseed oil, propylene glycol, lanolin, These agents are only effective while present on the skin; once removed, the TEWL returns to the previous level. Interestingly, it is not desirable to decrease TEWL by more than 40% because maceration with increased levels of bacteria can result. Therefore, occlusives are usually combined with humectant ingredients (Goldsmith et al., 2012).

4. Conclusion

Urea is an effective and safe treatment to increase skin hydration, decrease SCORAD, decrease TEWL although not as well as ceramide. The most common sensations that appear after urea treatment are redness, stinging and smarting. This is not irritation in the ordinary sense and usually does not cause clinically noticeable damages to the skin, but the disagreeable sensations will reduce compliance, especially in children. They will preferred the ceramide-based cream over the urea cream as their daily moisturizer. Ceramide has been shown to be more effective and less irritating than urea. Ceramid can be quite expensive, while urea is a moisturizer that is easily found and accessible to the public.

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All work was done by all authors.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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