Original article

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Non-steroidal Topical Medications in the Treatment of Atopic Dermatitis in Children

The article deals with the problem of atopic dermatitis (AD) in children. The high prevalence of this pathology and a significant social and economic damage are responsible for the relevance of search for new drugs for the treatment of this pathology, which will accelerate the achievement of remission, disease process and prolong relapse. Inclusion in the basic therapy means of care for patients with AD of any severity in remission, and in aggravation has been a necessary element of therapy that can improve the effectiveness of treatments, shorten its duration, lengthen the period of remission, reduce the number of exacerbations, and reduce the need for topical steroids.

***Key words**: atopic dermatitis treatment, topic steroid, emollients, children.*

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Atopic dermatitis (AD) is a chronic allergic inflammatory disease of the skin accompanied by itching, age-related morphology of skin rash appearance and different stages of the disease. Its distinctive features in the pediatric population are not only more prevalent, but are also responsible for significant social and economic damage, including poor quality of life of patients and their parents, maladjustment, significant limitation of daily activity of children, missing work and school.

The clinical picture, seasonal displays (может лучше manifistations), and age characteristics of a typical arrangement of morphologic elements usually do not cause difficulties in correct diagnosis and timely administration of therapy by a skilled clinician. A stepwise approach to treatment, relapse prevention regulations which are elimination mode and hypoallergenic diet are currently known not only

to allergists, and also to pediatricians.

An integral part of the complex of cutaneous manifestations in AD is dry skin. Leather is a natural barrier that protects against the penetration of environmental factors and prevents moisture loss. AD causes disturbances epidermal cells differentiation and lipid composition of the epidermis, resulting in increased permeability to allergens, the immune reaction and start the inflammatory cascade in the dermis.

An important component of keratin cytoskeleton, providing structural integrity of the skin is a protein filaggrin; its degradation products bind water, thus preventing its cross epidermal loss. Studies have shown that filaggrin mutations are a risk factor for AD- its earlier, severe and recurrent stages, as well as for high levels of systemic atopic sensitization. Mutations in the gene filaggrin affect different its portions, and their incidence and prevalence vary in different regions of the globe. It should be noted that these mutations are responsible for up to 42% of atopic dermatitis [1, 2]. It is possible that a key role in the barrier function of the skin plays a serine proteinase inhibitor LEKTI (Lymph-Epithelial Kazal-type inhibitor) by inhibiting the activity of kallikrein (KLK), and thus regulating desquamation process. There is no doubt that the features of the immune response are low expression of interleukin (IL) 23, down expression of filaggrin down regulation by IL-4, IL-13 and 25, the last potentiate existing violations of barrier function, increase trans epidermal water loss and increase the permeability for the aggressive influence of environmental factors [3, 4].

In normal healthy skin lipid composition has the following ratios: Ceramides - 37%, cholesterol - 32%, free fatty acids -16% and esters of cholesterol-15%. In AD stratum cornea lipid composition changes: reduces number and impaired balance between different factions of Ceramide, increases the content of free cholesterol, and reduces the number of long-chain free fatty acids. All this leads to a violation of the formation of lamellar bodies and granules, increased protease activity and reduced Ceramide production.

Thus, the multiple pathogenesis of AD causes inclusion in the basic therapy of diseases of basic care, which may reduce the cross epidermal water loss due to occlusion properties, and extending into the stratum cornea - the deficit of lipids. The use of emollients (moisturizers) for patients with AD of any severity (as in remission, and in the exacerbation) should be a necessary step therapy, which will increase the effectiveness of therapy, reduce the duration of treatment, lengthen the period of remission, reduce the number of exacerbations, reduce need for active therapy, including topical steroids, an improve skin condition and prognosis. Restoration of the epidermal barrier of the skin is optimally combined with the physiological Ceramides, cholesterol and free fatty acid (FFA) - 3:1:1 or 1:1:1. A

tool for basic therapy AD Locobase Repair contains Ceramide III, cholesterol and free fatty acids (oleic and palmitic) in a 1:1:1 ratio, which ensures rapid recovery of the epidermal lipid barrier.
The aim of the study was to assess the efficacy and safety of topical use Locobase Repair 1-2 times a day compared with the drug Atoderm 2 times a day for 1 year in children aged 6 months to 12 years with atopic dermatitis of moderate severity.

Description of studied drug

The cream Locobase Repair is made of the following engredients: petrolatum, water, paraffin, liquid paraffin, glycerol, sorbitan oleate, carnauba wax, cholesterol, Ceramides 3, oleic acid, palmitic acid, carbomer, tromethamine.
Product: Tubes of 30 g.
The cream Atoderm is made of: Vaseline-glycerol complex in dispersed state, the sodium salt of ethylenediaminetetraacetic acid, vitamin E, phenoxyethanol, parabens.

Product: Bottles of 200 ml.

Patients and Methods

There have been an open randomized clinical trial in parallel groups. At the Institute of Preventive Pediatrics and Rehabilitation Scientific Center of Children 's Health RAMS 44 children aged 6 months to 12 years with atopic dermatitis of moderate severity (severity score SCORAD ≥ 20 and ≤ 60 points) had been followed for 1 year. As a basic therapy the patients received on the testimony (удалить!) 0.1% hydrocortisone cream 17-butyrate (Lokoid) 1-3 times a day. All the children were randomly assigned into 2 groups of 22 people each. Patients of the 1^{st} group, except for topical steroid medication, received Locobase Repair received once daily; and the children of the 2^{nd} group as means of care used Atoderm 2 times a day. The study did not include children with a primary episode of atopic dermatitis with exudation in the foci of inflammation, not allowing them to use ointment formulations, with hypersensitivity to any components of the studied drugs in the presence of secondary infection of the skin. Also under surveillance were not taken the children treated with phototherapy, immunosuppressive, cytotoxic agents, systemic corticosteroids, inhibitors of kaltsineyrin, and emollients to Ceramides in the previous month. According to the study protocol topical corticosteroid therapy was prohibited during the previous 7 days; children with severe somatic diseases, infectious and oncological diseases were also excluded from the study.
Patients were excluded from the study in the absence of positive dynamics of therapy within 14 days of drug Lokoid 1-3 times a day (clinical failure) or the development of secondary skin infections that required use of local or systemic

antibiotic therapy. In the event of adverse events, or states, demanding the abolition of any of the study drugs, and / or destination therapy, contrary to protocol, patient participation in research was also stopped.
After turning the patient in the study determination of the severity of AD according to scale SCORAD, assessment of quality of life (Children's Dermatology Life Quality Index (CDLQI, and a study of the skin by objective methods (ultrasound) were made. Parents' patients were taught keeping a diary with monitoring symptoms. Follow-up visits were carried out (in case of worsening - the first week - 2 times a week, then 1 time a week during remission - once a month) for one year. Further evaluation of the quality of life and the study of skin barrier function by objective methods were once every 3 months.
Evaluation of the drug effectiveness was carried by the following parameters:
• differences between the values of SCORAD at the start of the study and at the end of his/her participation;
• the total duration of periods of remission and periods of exacerbation;
• differences between the indicators of quality of life (on a scale CDLQI) of patients at enrollment into the study and at the end of his/her participation;
• the need to use topical steroids at the time of inclusion in the study and the patient at the end of his participation;
• the safety of therapy with the comparison.
The criterion for the effectiveness of treatment served as the achievement of positive clinical results in a reduction or complete resolution of itching, inflammation of the skin and the positive dynamics of instrumental methods of examination of the skin. For an objective assessment of the severity of atopic dermatitis and efficacy of therapy all patients were observed by using the index SCORAD (Severity Scoring of Atopic Dermatitis).
• Clinical cure - complete resolution of the skin process.
• Significant improvement - decrease of SCORAD index of at least 75% compared with the original data.
• Improvement - decrease of SCORAD index less than 75% but more than 25% compared with the original data.
• No change - decrease of SCORAD index less than 25%, or no change from baseline data.
• Deterioration - increased involvement of the skin in the pathological process in comparison with the original data.
Assessing quality of life questionnaire was carried out with the quality of life CDLQI. The following parameters were evaluated: symptoms and feelings, leisure, interpersonal relationships, therapy, school (for children older than 7 years) and rest, and sleep. The degree of reduction in quality of life was assessed as a

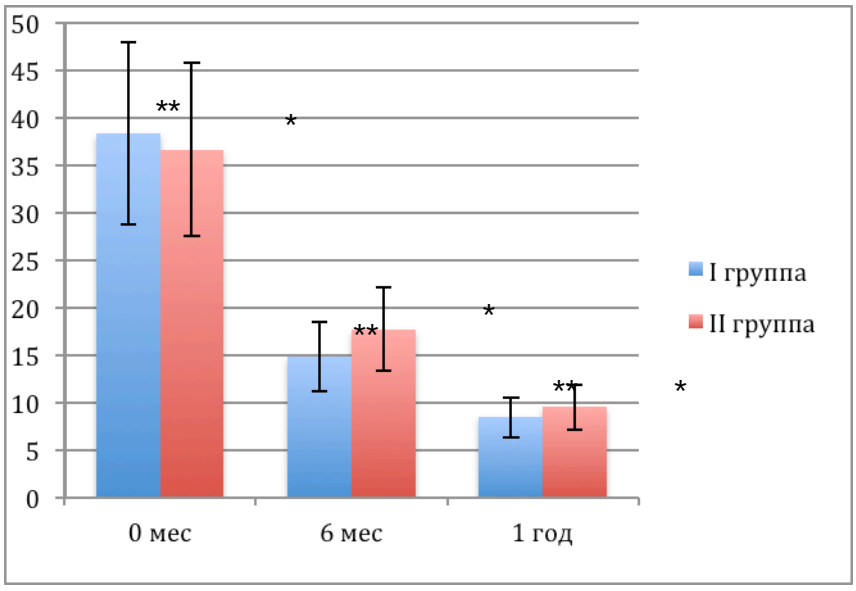
percentage.
The study used a statistical analysis system SAS (software package, SAS Institute, USA, version 8.02 for Windows XP). Testing quantitative traits for normality of distribution was carried out by using the Shapiro-Wilk criteria. Testing the hypothesis of equality of variances was carried out by using the criteria of Leuven. Description of quantitative traits, corresponding to normal distribution is presented as mean ± standard deviation; the symptoms are different from the normal distribution - in the form of the median, 25-75% quartiles.
Comparison of quantitative traits, satisfying the conditions of a normal distribution and equality of variances were performed by using Student's t-criteria. For comparison of quantitative traits that do not satisfy the conditions of a normal distribution or equality of variances, we used Wilcoxon-Mann-Whitney criteria. For comparison of paired quantitative traits satisfying a normal distribution and equality of variances, we used paired Student's t-criteria, for not satisfying the conditions of a normal distribution or equality of variances was used Wilcoxon test for paired comparisons.

Results of the study

The study included 44 children aged 6 months to 12 years old with atopic dermatitis of moderate severity (SCORAD ≥ 20 and ≤ 60 points). Gender distribution was 20 boys and 24 girls (45.5 and 54.5%, respectively). The form of cutaneous manifestations of the process occurred predominantly as erythematous-squamous and lichened.
The first group consisted of 22 children, but later a child was excluded from the study due to the addition of a respiratory infection on the background of a sharp aggravation of the disease. As an external therapy in the group the cream Lokoid and ointment Locobase Repair was applied. During the period of exacerbation Lokoid used 2 times a day for 7 days, then 2 times a week for 14 days, the ointment Locobase Repair - 1 per day. The median SCORAD index at enrollment of patients in the study was 38, 3 ± 1, 9 points (95% CI 34, 39-42, 2).
The second group consisting of 22 children was randomized, but 1 patient was excluded from the study due to protocol violation, and two children dropped out of the surveillance program due to the worsening of the skin process, which required the combined use of local therapy.
Thus, II group consisted of 19 patients with atopic dermatitis of moderate severity of erythematous-squamous or lichened form treated by a moisturizer cream Atoderm 2 times a day throughout the study period. Cream Lokoid was used during the exacerbation, 2 times a day for 7 days, and then 2 times a week for 14 days. The median SCORAD index was 36, 6 ± 2, 05 points (95% CI: 32, 5-40, 8).
Systemic therapy in both groups was of antihistamines (cetirizine, levocetirizine)

in dosages for age.
At each visit we measured consumption of steroids and moisturizers.
Within 7 days of prescribed therapy for children both groups showed marked improvement. By the end of the 1-month observation of patients in both groups showed a significant decrease in the index SCORAD, improved quality of life based on the results of the questionnaire, reducing the consumption of topical steroids.
After 6 months of therapy, the mean value of SCORAD index in Group I was 14,8 ± 1,6 points (95% CI: 11,1-18,4), and after 1 year of observation, this figure dropped to 8,4 ± 0,9 (95% CI 6,3-10,4). In group II the mean value of SCORAD index was 17, 7 ± 1, 9 (95% CI: 14, 0-21, 0) and 9, 5 ± 1, 0 (95% CI 6, 7-12) at 6 months and 1 year, respectively (Fig. 1). Thus, in both groups index SCORAD (p <0, 0001) was significantly reduced.
In Group I, the total decrease in SCORAD as compared with the average at enrollment was 78%, which corresponds to a significant improvement. In the second group based on their performance improvement in the SCORAD index was fixed at 74%, which corresponds to clinical improvement. In addition, the total duration of periods of remission for the group I was 11.5% higher than in group II (the number of days that the patient did not require the use of ointment Locobase Repair).

Fig. A. Dynamics of the SCORAD index in the study groups



Notice: * And ** - p <0, 0001, * - a comparison index SCORAD index dynamics in 6 months and 1 year in group I, and ** - in the group II.

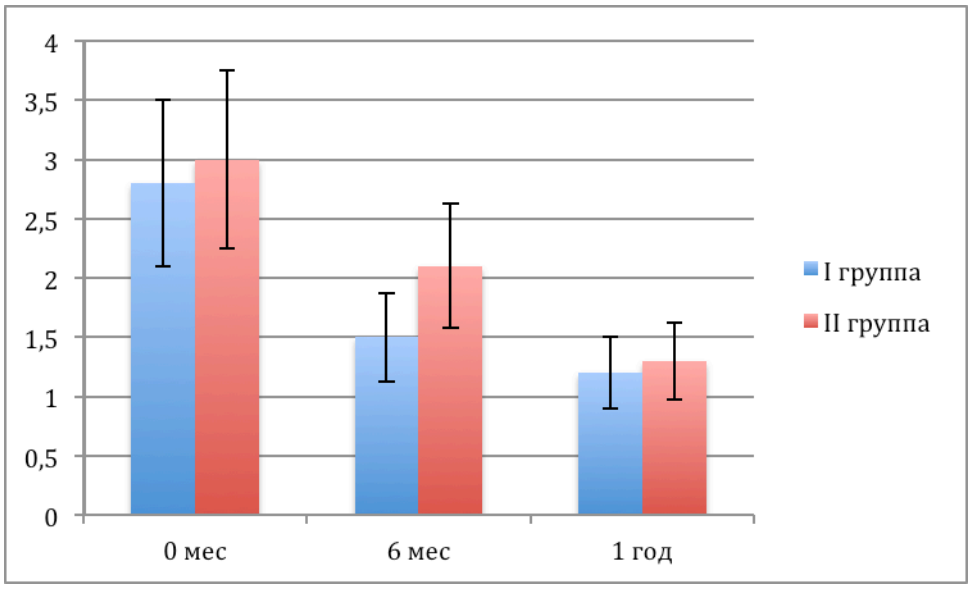
Clinically, a decrease in the recurrence of the disease and the severity of the current 1-year follow-up was observed. Deterioration process of the skin was provoked by errors in diet, taking medications for comorbid illnesses, and stressful situations.

The study analyzed the use of topical steroid consumption by patients. The calculation of daily consumption of cream Lokoid conducted by the following formula with rounding to the fold:

amount of the drug (r) = area of lesion (cm2) × 0, 00154 × application frequency (once daily).

In Group I the following dynamics of the average daily consumption of topical steroid were identified: 2,8 ± 0,3 g (95% CI 2,2-3,4) on the first visit, 1.5 g ± 0,12 g (95% CI 1.1-1.9) at 6 months and 1,2 ± 0,13 g (95% CI 0,9-1,6) after 1 year of observation (p <0.05). In Group II patients also had a tendency to reduce consumption: on the first visit, the daily consumption was 3,0 ± 0,33 g (95% CI 2,25-3,75), after 6 months of follow-2,1 ± 0,2 g (95% CI 1.6-2.6), and after 1 year from the start of the study - 1,3 ± 0,19 g (95% CI 0,98-1,6). The observed decrease in the use of topical steroids with regular use of moisturizer was significant: p <0, 05 (Fig. 2).

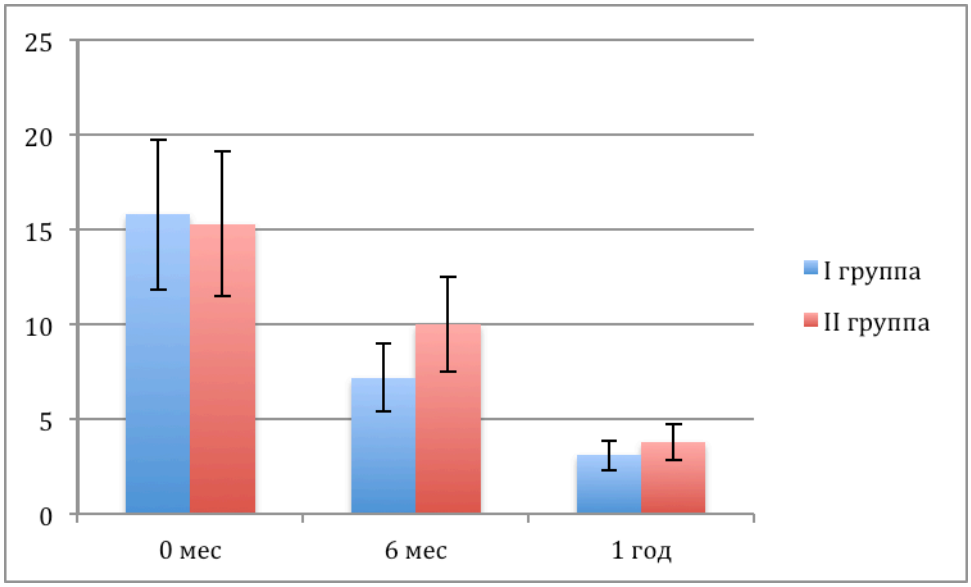
Fig 2: The dynamics of the daily consumption of topical steroid in the study



Throughout the observation of parents' patients and children themselves reported improved quality of life: reduction of subjective symptoms of itching and burning, reduce anxiety and discomfort, social maladjustment. The degree of reduction of quality of life questionnaire CDLQI at the time of enrollment of patients in group I

was 15,83 ± 1,87% (95% CI: 12,0-19,7) and in patients of group II - 15,35 ± 1,69 % (95% CI: 11,9-18,8). After 6 months of starting treatment, patients of group I reduced quality of life index which was 7,2 ± 1,7% (95% CI 3,8-10,6), patients of group II - 10,0 ± 1,6 (95 6,7-13,3% CI). By the end of the study, all patients reported improved quality of life, the degree of reduction in quality of life amounted to 3,1 ± 0,4% (2,3-3,9 95% CI) in patients in group I and 3,8 ± 0,8% (95 % CI 2,1-5,5) - in patients of group II (Fig. 3).

In Fig 3: Dynamics of indicators of quality of life (CDLQI) patients in the study AD



Ultrasound examination of the patients' skin intradermal increased arterial blood flow and the presence of hypo echoic stripe in the upper part of the dermis were detected in both groups at the first visit. Within 1 month of therapy in both groups increased venous blood flow was showed, a gradual decrease in skin thickness, and normalization of its echo structure and echogenicity. Intradermal arterial blood flow was significantly decreased, and then not recorded, hypo echoic band disappeared in the superficial layer of the dermis (in the absence of the resumption of the patient's skin rash), swelling, and decreased infiltration, indicating that the transition process was in the sub acute stage.

The results of the study investigated the use of drugs in children aged 6 months to 12 years with atopic dermatitis of moderate severity showing high efficacy and

safety of these means. Adverse events associated with the use of study resources have not been recorded.

The following positive results (according to the index SCORAD) were identified: reduction of dryness and desquamation, a complete or partial relief of the inflammatory process, the absence of itching and a significant improvement in quality of life of patients in both groups (based on questionnaire CDLQI; decrease in consumption of topical steroids, as well as improvement of skin on the basis of ultrasound examination.

Analysis of the data indicates a more rapid decrease in SCORAD index in the group of children treated with topical steroid medication plus Locobase Repair. The trend toward more pronounced steroid-saving effect, improving the quality of life, according to dermatological questionnaire for children CDLQI during the observation characterized patients of the 1st group.

There is no doubt that the use of specialized emollients in the treatment of patients with atopic dermatitis not only restores the barrier function of skin, but also makes it easier to achieve remission of the disease, longer control the disease process and reduce the need for the application of topical steroids.

Literature:

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