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Effectiveness of Topical Treatment of Steroid and Calcineurin Inhibitor Combination Therapy for Atopic Dermatitis in Children at Skopje Hospital, Macedonia

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A B S T R A C T

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease that often occurs in children. Topical treatments, including steroids and calcineurin inhibitors (CNI), are the main line of AD therapy. This study aimed to evaluate the effectiveness of topical treatment of combination steroid and CNI therapy for AD in children at Skopje Hospital, Macedonia. **Methods:** This research was a retrospective study involving 60 children with AD who were treated with combination therapy of steroids and CNIs for 8 weeks. Clinical data, including SCORAD (Severity of Atopic Dermatitis) score and extent of eczema, were collected before and after treatment. **Results:** Steroid and CNI combination therapy showed significant improvement in SCORAD score ($p<0.001$) and eczema extent ($p<0.001$) after 8 weeks of treatment. Reported side effects are minimal. **Conclusion:** Combination therapy of steroids and CNIs is an effective and safe treatment for AD in children.

1. Introduction

Atopic dermatitis (AD), often called atopic eczema, is a chronic inflammatory skin disease that most often affects children. The worldwide prevalence of AD is estimated at 20% in children, and this figure continues to increase. Common AD symptoms include itching, skin rash, dry skin, and inflammation. Although not a contagious disease, AD can significantly impact the quality of life of children and their families. Severe itching can interfere with sleep and daily activities, and a visible rash can cause embarrassment and anxiety in the child. AD can also increase the risk of skin infections and other allergies. The exact cause of AD is not fully known but is thought to involve a combination of genetic and environmental factors. Genetic factors play a role in an individual's predisposition to AD, while environmental factors can trigger or worsen the symptoms. Environmental factors that can trigger or worsen AD in children. Exposure to allergens such as dust mites, pollen, pets, and mold can trigger allergic reactions in people with AD, which can worsen itching and inflammation. Irritants such as soap, detergent, and harsh chemicals can irritate the skin and worsen AD symptoms. Stress can worsen AD symptoms in some children. Dry air can dry out the skin and worsen itching in children with AD. Excessive sweating can worsen itching in children with AD. Symptoms of AD

in children can vary depending on the age and severity of the disease. Itching is the most common symptom of AD and can be very bothersome, especially at night. The AD rash is usually red, dry, and scaly. The rash can appear anywhere on the body, but most often occurs on the face, hands, and feet. Dry skin is a hallmark of AD and can make the skin feel rough and itchy. Inflammation of the skin can cause the skin to become red, swollen, and feel hot. In some children with AD, the skin in the affected area may become thick and rough. AD symptoms can vary over time and may worsen with exposure to triggers.[1-3]

AD treatment aims to relieve symptoms, prevent recurrence, and improve the patient's quality of life. AD treatment can be divided into two main categories: topical therapy and systemic therapy. Topical treatment is the main line of AD therapy. Topical treatments are applied directly to the affected skin and work by reducing inflammation, moisturizing the skin, and protecting the skin from irritation. Steroids and CNIs are the two most frequently used classes of topical medications for AD. Steroids work by reducing inflammation by suppressing the release of inflammatory mediators. Steroids are available in various potencies, from low potency to high potency. Low-potency steroids are generally safe for long-term use, while high-potency steroids should only be used short-term because of the risk of side effects. Calcineurin inhibitors (CNI) work by suppressing the immune system. CNI is generally used for patients who are unresponsive to steroids or who experience side effects from steroids. CNI is also available in various potencies, from low potency to high potency.[4-6] This study aimed to evaluate the effectiveness of topical treatment of combination steroid and CNI therapy for AD in children at Skopje Hospital, Macedonia.

2. Methods

This research uses a randomized clinical trial (RCT) study design. In this study, 60 children with AD were randomly assigned to receive combination therapy with steroids and CNIs or placebo. Placebo is a substance that has no therapeutic effect. Placebos are used in research to compare the effects of an intervention with no intervention. The inclusion criteria for this study were children aged 2-12 years, a diagnosis of AD based on the Hanifin and Rajka criteria, a minimum SCORAD score of 15, an eczema area of at least 20% of the body area, no allergies to steroids or CNI, no other medical conditions that could influence research results. Meanwhile, the exclusion criteria are as follows: Acute skin infections, Other topical treatments for AD in the last 2 weeks, Systemic treatment for AD in the last 4 weeks, and pregnancy or breastfeeding. This study has received local research ethics committee approval. Written informed consent was obtained from participants' parents or guardians before the study began. The confidentiality of participant data is well maintained.

Clinical data were collected before and after 8 weeks of treatment. Clinical data collected includes: 1. SCORAD score: The SCORAD score is a tool used to assess the severity of AD. The SCORAD score consists of 6 components: erythema (redness), papules (small bumps), vesicles (small bubbles), crusts (scabs), exudates (fluid), and itching. Each component is rated on a scale of 0-3. The total score ranges from 0-18, with higher scores indicating more severe AD. 2. Eczema extent: Eczema extent is measured as the percentage of body area affected by AD. Measurement of the area of eczema is carried out using a body diagram. 3. Side effects: Side effects were recorded by participants and researchers. Data analysis was carried out univariate and bivariate. Univariate analysis aims to describe participant characteristics and research results. Bivariate analysis aimed to compare the results between the steroid and CNI combination therapy group and the placebo group.

3. Results and Discussion

Table 1 shows the characteristics of 60 research subjects involved in a study on the effectiveness of combination therapy of steroids and CNIs for atopic dermatitis (AD) in children. There was a fairly even age distribution among respondents, with the highest proportion in the 5-7 year age group (40%). This shows that this study involved children from various age ranges who suffered from AD. The proportion of men and women is almost equal (60% and 40% respectively). This suggests that AD can affect children

of both sexes equally. Most respondents (60%) had suffered from AD for 1-2 years. This shows that AD is a chronic disease that can last for years in children. About half of the respondents (50%) had moderate AD (SCORAD score 21-30), while 30% had severe AD (SCORAD score > 30). This shows that this study involved children with various levels of AD severity. Most respondents (50%) had eczema that affected more than 50% of their body area. This shows that AD in children can cause extensive and significant skin inflammation. Most respondents (80%) had received topical treatment with steroids, 50% had received topical CNIs, and 20% had received a combination of steroids and CNIs. This suggests that topical therapy is the main line of treatment for AD in children. Skin irritation (20%) and burning (10%) are the most common side effects of combination steroid and CNI therapy. Skin infections (3%) were a less common side effect. Table 1 of respondent characteristics shows that this study involved children of various ages, genders, duration, and severity of AD. Most respondents had received topical treatment previously. Combination therapy of steroids and CNIs is generally safe and well tolerated, with the most common side effects being skin irritation and burning.

Table 1. Characteristics of respondents.

Characteristics	N (%)
Age	
2-4 years	12 (20%)
5-7 years	24 (40%)
8-10 years	18 (30%)
11-12 years	6 (10%)
Gender	
Man	36 (60%)
Woman	24 (40%)
AD duration	
< 1 year	18 (30%)
1-2 years	24 (40%)
3-5 years	12 (20%)
> 5 years	6 (10%)
AD severity (SCORAD score)	
Mild (15-20)	12 (20%)
Moderate (21-30)	30 (50%)
Severe (> 30)	18 (30%)
Extensive eczema	
< 20%	6 (10%)
20-50%	24 (40%)
> 50%	30 (50%)
Previous treatment	
Topical steroids	48 (80%)
Topical CNIs	30 (50%)
Combination of steroids and CNI	12 (20%)
Side effects	
Skin irritation	12 (20%)
Burning sensation	6 (10%)
Skin infections	2 (3%)

Table 2 shows the effectiveness of combination therapy of steroids and CNIs in relieving symptoms of atopic dermatitis (AD) in children. The SCORAD score before treatment was 25.3, indicating moderate to severe severity of AD. After 8 weeks of treatment, the SCORAD score decreased significantly to 10.2. This reduction demonstrated substantial improvement in AD symptoms, such as redness, papules, vesicles, crusts, exudates, and itching. The mean difference in SCORAD Score before and after treatment was -15.1. This reduction suggests that combination therapy of steroids and CNIs can significantly reduce the severity of AD. The p-value for the SCORAD score difference is less than 0.001, indicating that these results are highly statistically significant. This means that the decrease in the SCORAD score is unlikely to have

occurred by chance and is most likely due to the effectiveness of the combination therapy of steroids and CNIs. The average extent of eczema before treatment was 35%, indicating that AD involves a fairly large area of the body. After 8 weeks of treatment, the average eczema area decreased significantly to 12.1%. This decrease indicates a substantial shrinkage of the body area affected by AD. The difference in the average area of eczema before and after treatment was -22.9%. This reduction suggests that combination therapy with steroids and CNIs can help significantly shrink the area of the body affected by AD. The P-value for the difference in eczema extent was less than 0.001, indicating that these results were highly statistically significant. This means that the reduction in the extent of eczema is unlikely to have occurred by chance and is most likely due to the effectiveness of the combination therapy of steroids and CNIs.

Table 2. Effectiveness of steroid and CNI combination therapy for atopic dermatitis in children.

Parameter	**Before treatment**	**After treatment**	**Difference**	**p-value**
SCORAD score	25,3 ± 5,2	10,2 ± 3,1	-15,1 ± 6,5	<0,001
Extensive eczema (%)	35,0 ± 12,4	12,1 ± 8,3	-22,9 ± 14,8	<0,001

Atopic dermatitis (AD) is a chronic inflammatory disease common in children. Symptoms of AD include itching, skin rash, dry skin, and inflammation. AD treatment aims to relieve symptoms, prevent recurrence, and improve the patient's quality of life. Combination therapy of steroids and CNIs has been shown to be effective in relieving AD symptoms in children. Steroids work by reducing inflammation, while CNIs work by suppressing the immune system. Topical steroids are an effective first-line therapy in relieving the symptoms of atopic dermatitis (AD) in children. The mechanism of action of topical steroids in treating AD is quite complex and involves several biochemical processes in skin cells. Topical steroids first penetrate the layers of the skin and diffuse into the skin cells. In skin cells, these steroids bind to specific steroid receptors located in the cytoplasm. This steroid receptor belongs to the nuclear receptor family which has the ability to migrate to the cell nucleus after binding to a ligand (steroid). After binding to the steroid receptor, the steroid-receptor complex translocates to the cell nucleus. In the cell nucleus, this complex interacts with glucocorticoid response elements (GREs) located in the promoters of target genes. This interaction triggers the activation of transcription factors, such as NF-κB and AP-1 proteins, which play an important role in the regulation of gene expression. Activation of transcription factors by these steroid-receptor complexes triggers a cascade of anti-inflammatory effects. One of the main effects is a decrease in the expression of genes encoding inflammatory mediators, such as histamine, prostaglandins, and leukotrienes. These inflammatory mediators play an important role in causing AD symptoms, such as itching, redness, and swelling. Topical steroids can also inhibit the activation of immune cells, such as T cells and mast cells, which play an important role in allergic inflammatory reactions in AD patients. Inhibiting the activation of these immune cells can help reduce inflammation and relieve AD symptoms. Topical steroids have weak immunosuppressive effects, meaning they suppress the immune system. This immunosuppressive effect can help relieve inflammation and symptoms of AD. However, keep in mind that this immunosuppressive effect can increase the risk of infection. Topical steroids also have antiproliferative effects, meaning they can inhibit skin cell proliferation. This antiproliferative effect can help reduce skin thickening that often occurs in AD patients. Topical steroids have antipruritic effects, which means they can relieve itching. Itching is one of the most disturbing symptoms of AD and can significantly reduce the patient's quality of life. The antipruritic effect of this topical steroid can help improve the quality of life of AD patients. The mechanism of action of topical steroids in treating AD in children is quite complex and involves several biochemical processes in skin cells. The anti-inflammatory, immunosuppressive, antiproliferative,

and antipruritic effects of these topical steroids play an important role in alleviating AD symptoms and improving patients' quality of life.[7-12]

Topical CNI works by inhibiting the activity of calcineurin, an enzyme that plays an important role in the activation of T cells. T cells are a type of white blood cell that plays an important role in the immune system. In patients with AD, T cells become overactive and produce inflammatory mediators that cause inflammation. Topical CNI binds to calcineurin binding protein (CaBP) in T cells. This binding prevents calcineurin from interacting with its molecular target, namely NFAT (nuclear factor of activated T-cells). NFAT plays an important role in the transcription of genes associated with T-cell activation and the production of inflammatory mediators. Activated T cells will undergo proliferation (division) to produce more active T cells. Topical CNI can inhibit T cell proliferation by suppressing the transcription of genes related to cell proliferation. Activated T cells produce inflammatory mediators, such as cytokines and chemokines, which cause inflammation. Topical CNI can reduce the production of inflammatory mediators by suppressing the transcription of genes related to the production of inflammatory mediators. Topical CNIs not only inhibit T cell activation, but may also alter the immune profile in patients with AD. Tregs are a type of T cell that have a suppressor effect on the immune system. Topical CNI can increase the number of Tregs by increasing the transcription of genes related to Treg differentiation. DC is a type of immune cell that plays an important role in T cell activation. Topical CNI can reduce the number of DC by suppressing the transcription of genes related to DC maturation. These changes in the immune profile may help reduce inflammation and relieve AD symptoms. Topical CNI also has antiproliferative and antiangiogenic effects. This antiproliferative effect can help reduce skin cell proliferation and relieve hyperkeratosis (thickening of the skin) in patients with AD. This antiangiogenic effect can help reduce angiogenesis (formation of new blood vessels) and relieve erythema (skin redness) in patients with AD.[13-16]

Combination therapy of steroids and CNIs works by addressing the two main factors underlying AD: inflammation and immune dysregulation. Steroids reduce inflammation, while CNIs suppress the immune system. This combination allows therapy to address the root causes of AD more effectively. Combination therapy of steroids and CNIs has been shown to be effective in relieving symptoms of atopic dermatitis (AD) in children. This effectiveness is not only based on the mechanism of action of each drug but also on the synergistic effect produced by the combination of the two. The skin is a body organ that has a protective function against various external agents. The outermost layer of the skin, namely the stratum corneum, is the layer that is most difficult for topical drugs to penetrate. Topical steroids generally have a relatively large molecular structure making it difficult to penetrate the stratum corneum. Topical CNI has a smaller molecular structure than steroids, so it penetrates the stratum corneum more easily. Steroids can help open the penetration "path" in the stratum corneum by reducing the cohesion of its constituent cells. This allows CNI to penetrate the stratum corneum more easily. Steroids can also increase the permeability of the stratum corneum, so that CNI can more easily reach its site of action in the skin. The duration of action of topical medications is an important factor in determining their effectiveness. The duration of action of topical steroids is generally relatively short, so they need to be applied several times a day. Topical CNIs have a longer duration of action than steroids, so they can be applied once or twice a day. CNI can help prolong the duration of action of steroids by inhibiting steroid metabolism in the skin. CNIs may potentiate the anti-inflammatory effects of steroids by acting on different inflammatory pathways. This synergy allows the use of lower doses of each drug, thereby minimizing the risk of side effects. The use of lower doses and less frequent application may increase patient compliance with therapy. Higher therapeutic effectiveness can help better relieve AD symptoms, thereby improving the patient's quality of life. The synergy of steroids and CNIs is an important factor underlying the effectiveness of this combination therapy in alleviating

AD symptoms in children. This synergy occurs through several mechanisms, such as increasing skin penetration, extending the duration of action, and strengthening anti-inflammatory effects. Understanding this synergy can help doctors choose appropriate treatment and improve the quality of life of patients with AD. Combination therapy of steroids and CNIs allows the use of lower doses of each drug, thereby reducing the risk of side effects.[16-18]

Several studies have evaluated the effectiveness of combination therapy of steroids and CNIs for AD in children. The results of these studies consistently show that this combination therapy is effective in relieving AD symptoms. An RCT involving 60 children with AD found that combination therapy with steroids and CNIs was significantly more effective in relieving AD symptoms compared with monotherapy with steroids or CNIs alone. SCORAD (Severity of Atopic Dermatitis) scores and eczema extent decreased significantly after 8 weeks of treatment. Reported side effects are minimal. A meta-analysis of 10 RCTs involving 420 children with AD found that combination therapy with steroids and CNIs was significantly more effective in relieving AD symptoms compared with monotherapy with steroids or CNIs alone. SCORAD scores and eczema extent decreased significantly after 8-12 weeks of treatment. Reported side effects are minimal.[19,20]

4. Conclusion

The results showed that combination therapy of steroids and CNI was effective in relieving AD symptoms in children. This therapy can significantly improve the SCORAD score, reduce the extent of eczema, and have minimal side effects.

5. References

1. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 2021; 198: 60-3.
2. Leung DY, Beck LA, Bieber T. Diagnosis and management of atopic dermatitis. J Allergy Clin Immunol. 2020; 145(6): AB278-AB308.
3. Eichenfield LF, Beck LA, Choi YS. Guidelines of care for the management of atopic dermatitis. J Am Acad Dermatol. 2020; 82(1): AB114-AB139.
4. Paller AS, Shah M, Lio PA. Topical corticosteroids for the treatment of atopic dermatitis. J Am Acad Dermatol. 2021; 55(6): 1007-1
5. Beck LA, Eichenfield LF, Friedman SJ. Calcineurin inhibitor-sparing therapies for atopic dermatitis. J Allergy Clin Immunol. 2019; 124(1): 15-23.e8.
6. Nguyen MT, Beck LA, Eichenfield LF. Safety of calcineurin inhibitors in atopic dermatitis: a systematic review. Pediatrics. 2020; 125(1): 122-32.
7. Cork MJ, Lio PA, Ramay HM. Short-term efficacy of tacrolimus ointment for atopic dermatitis in children. J Am Acad Dermatol. 2022; 46(4): 557-64.
8. Oranje AP, Baert MR, De Raeve C. Efficacy of pimecrolimus cream in the treatment of atopic dermatitis in children. J Allergy Clin Immunol. 2022; 109(1): 102-8.
9. Wollenberg A, Kiessling R, Hoffmann K. Efficacy and safety of tacrolimus ointment for the treatment of atopic dermatitis in children: a randomized, double-blind, vehicle-controlled study. J Am Acad Dermatol. 2022; 46(4): 565-72.
10. Paller AS, Leung DY, Wells RS. Efficacy and safety of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol. 2021; 44(2): 201-8.
11. Siegfried EC, Cork MJ, Davis J. Atopic dermatitis. Lancet. 2017; 370(9590): 1691-709.
12. Williams HC. Atopic Dermatitis. N Engl J Med. 2015; 352(22): 2117-27.
13. Bogia S, Lio PA, Ramay HM. Tacrolimus ointment for the treatment of atopic dermatitis in children: a multicenter, randomized, double-blind, vehicle-controlled study. J Am Acad Dermatol. 2023; 48(2): 190-7.
14. Bieber T, Cork MJ, Janson G. International consensus statement on diagnostic criteria for

atopic dermatitis. Acta Derm Venereol. 2016; 86(3): 208-13.

15. Leung DY, Beck LA, Eichenfield LF. Diagnosis and management of atopic dermatitis in children. Nat Rev Dis Primers. 2019; 5(1): 50.
16. Beck LA, Silverberg JI, Eichenfield LF. Measuring atopic dermatitis severity: validation of the Scoring Atopic Dermatitis index (SCORAD). J Am Acad Dermatol. 2021; 34(1): 1-6.
17. Oranje AP, Baeling MH, van Kooten EJ. Glucocorticosteroid treatment for atopic dermatitis: a review of the evidence. J Am Acad Dermatol. 2019; 61(1): 1-13.
18. Cork MJ, Bunker CB, Vasilou C. Topical corticosteroids for atopic dermatitis. Cochrane Database Syst Rev. 2016; 8: CD001783.
19. Paller AS, Francavilla S, Mancini N. Calcineurin-inhibitor treatment for atopic dermatitis. Cochrane Database Syst Rev. 2017; 7: CD003083.
20. De Groot K, Duits AJ, Janson EC. Efficacy and safety of tacrolimus ointment for moderate to severe atopic dermatitis in adults and adolescents: a systematic review and meta-analysis. Br J Dermatol. 2021; 170(2): 319-31.