Comparative clinical efficacy and safety of coded herbal medicine dermovix in the management of patients with atopic dermatitis versus allopathic medicine

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Abstract: Atopic dermatitis (AD) is defined as a chronic, highly pruritic inflammatory condition of skin. It is estimated that this disease may lead significant morbidity and also adversely affects the quality of life. Atopic dermatitis responds well to home treatment. Proper skin care reduces the need for medicines. Topical creams and oral antihistamines can be used to suppress the symptoms. The clinical trial was conducted on 60 patients in which 30 are control and 30 are test by taking written consent from them. Dermovix significantly improved skin symptoms associated with AD. This Dermovix ointment was safe and well tolerated in specified age group patients. Overall results of individual group were analyzed by using Paired sample t-test and level of significance of all the symptoms was calculated. Both the drugs showed similar efficacy and the calculated p value was $p<0.05$. Except in case of dry skin the test drug had shown not significant p value i.e. 0.407. When we compare all these and their effects and patients' complaints then *Test group* have shown better results because of no side effects.

Keywords: Atopic dermatitis, topical cream, clinical trials.

INTRODUCTION

Atopic dermatitis (AD) is defined as a chronic, highly pruritic inflammatory condition of skin. It is more prevalent in children (Krakowski *et al.,* 2008). The disorder may cause the morbidity and lasts adverse affects on the quality of life (McKenna and Doward, 2008)). Atopic dermatitis also exert huge economic burden in developed countries also (Barbeau and Bpharm, 2006). In fact, atopic dermatitis is frequently the preliminary step in the "atopic march", which leads to the asthma and allergic rhinitis in the mainstream of the agonize patients (Spergel and Paller, 2003). Recent research in atopic dermatitis suggests that structural abnormalities of skin and immune dysregulation are major pathwaly for disease pathology (Boguniewicz and Leung, 2010).

As it is condition characterized by chronic inflammatory state of disease, related to other skin diseases like allergic rhinitis, allergic conjunctivitis and asthma. Usually atopic dermatitis first appears before the age 2, but can also first appear during adulthood. The extent of lesions varies depending on the age of patients; on cheeks during infancy, in flexures in adolescence while in adulthood it will manifest itself in the face, neck, upper part of thorax and around the wrists and also in the flexures. This requires treatment during longer periods of time for the patients, which would involve periods with extreme itching, impaired sleep at night and difficulties concentrating which in their turn would affects the patients, or patients family quality of life. The eczema of some patients is so serious that they have to be in hospital care. Atopic dermatitis is a complex genetic disease, since it develops interaction between different genes and the environment. The diseases genes encoding are two major groups of elements; epidermal or other epithelial structural proteins and important elements of the immune system (Bieber, 2008).

It is the first disease to present in a series of allergic diseases that may involve food allergy, respiratory problems etc in order has given rise to the "atopic march" theory, which suggests that AD is part of a progression that may lead to subsequent allergic disease at other epithelial barrier surfaces (Spergel, 2010; Carlsten *et al.*, 2013). It is the most common chronic disease in infants the cumulative incidence for children up to seven years of age has increased dramatically from 3% in the 1960s to approximately 19% in 1990s (Olesen *et al.*, 1997; Schultz and Hanifin, 1992). Atopic dermatitis seems to coincide with affluence of the population (Williams *et al.*, 1999; von Mutius *et al.*, 1998) and the growing burden of the disease has a substantial impact on health and quality of life on the individual patient as well as on the family (Ben Gashir *et al.*, 2004; Lawson *et al.*, 1998), as well as having a significant socioeconomic impact due to treatment costs and loss of parental productivity (Weinmann *et al.*, 2003; O'Connell, 2004).

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The prevalence of atopic dermatitis increased dramatically in the last half of the twentieth century, becoming a major health problem in many countries. The increase began first in the most developed nations, and as nations' standards of living have increased worldwide, so has the prevalence of atopic dermatitis. Rates of atopic dermatitis are around 30% in the most developed nations and exceed 10% in many countries, resulting in a worldwide cumulative prevalence of 15-20%. In the most developed nations, the rates of atopic dermatitis plateau in the 1990s, whereas developing nations have rates that continue to increase. Other factors associated with high rates of atopic dermatitis are high latitude (perhaps associated with low levels of annual sun exposure) and lower mean annual temperature. A role for exposure to allergens thought to "trigger" atopic dermatitis is not supported by epidemiological studies. Iceland has a very high rate of atopic dermatitis (27%) yet has no dust mites, few trees, and low pet ownership. Children in Iceland, none the less, often have positive skin prick tests to environmental allergens (24%). This brings into question the value of such tests in predicting causal environmental allergens in atopic dermatitis. In some studies maternal smoking and the fact that two or more members of the household smoke are associated with higher rates of atopic dermatitis. Girls are slightly more likely to develop atopic dermatitis. In the US, there is increased risk of the atopic dermatitis during first 6 months of the life is noted in the infants with the African and Asian ethnicity, mainly affected male, greater gestational age at birth and a family history of atopy, particularly a maternal history of eczema. About 50% of cases of atopic dermatitis appear in the first year of life, the vast majority within the first 5 years of life, and the remaining cases of "adult" atopic dermatitis usually before age 30. Atopy is now so common in the population that most individuals have a family history of atopy. Elevated IgE levels are not diagnostic of atopic disease in the adult. Therefore, elevated IgE and a family history of "atopy" in an adult with new-onset dermatitis should not be used to confirm the diagnosis of "adult" atopic dermatitis. Rather, a dermatologist should uncommonly make the diagnosis of adult "atopic dermatitis" for a dermatitis appearing for the first time after age 30. Adult atopic dermatitis should only be considered when the dermatitis has a characteristic distribution and other significant diagnoses, such as allergic contact dermatitis, photo dermatitis and cutaneous T-cell lymphoma, have been excluded.

Diagnosis of atopic dermatitis

It is diagnosed by complete history and physical examination**.** It does not require specific laboratory test or histologic features, mainly based on history of the patients and their clinical manifestations. In 1980 Hanifin and Rajka (Svensson *et al.,* 1985) established a diagnostic set of criteria for atopic dermatitis, caused by a general lack of atopic dermatitis disease definition. They published a set of diagnostic criteria in which the diagnosis is based on 3 of 4 major criteria and 3 of 23 minor signs. The criteria are traditionally the most accepted international scientific diagnostic tool and are even referred to as gold standard when validating diagnostic criteria (Gu *et al.,* 2001).

Management

That management of atopic dermatitis include different ways to control and combat this disease, it include line of treatment and specific treatment.

Herbal treatment

The eastern/herbal coded medicine Dermovix is designed in such manner that it should cover treatment of atopic dermatitis from symptomatic point of view. Dermovix ointment have the potential to eradicate atopic dermatitis symptom demand provide strength to the live to function better. Dermovix components exert to decrease the symptom gradually and after 1month continuous use of Dermovix, symptom decreased to the negligible level and patient gets complete relief from disease.

Aims and objectives

To establish and evaluate scientific and clinical evidence of herbal/eastern formulation and find out the clinical safety and efficacy. To measure the clinical response of herbomineral formulation in patients of AD.

Methodology (patients and method

This study was carried out on patients of age 2 year to above 40 years. The patients are categorized into two different groups i.e. test group and control group on whom eastern/herbal coded formulation and allopathic formulation are applied respectively. The detailed history of the patients and questionnaire was documented on clinical trial proforma at every follow up visit under the supervision of monitor physician and supervisor. This research based study was prospective case controlled trial in which one group is selected as control group and one was selected as test group, for both groups all the conditions were similar.

Sample selection

The clinical trial was conducted on 60 patients in which 30 are control and 30 are test by taking written consent from them. These including all socioeconomic status patients at different health care centers i. e. at ShifaulMulk Memorial-Hospital and Al-Rasheed Darushifa Malkani Liaqut Pur. In this study project the patients were selected according to inclusion criteria. The patients are categorized into two different groups i. e. test group and control group on whom eastern/herbal coded formulation and allopathic formulation are applied respectively.

Table 1: Design strategy to explore atopic dermatitis

Number of drugs	1. Test drug 2. Control drug	1. Dermovix 2. Betnovate N-Cream
Total Patients	30+30	30 Test + 30 Control
Number of Tests	History, Physical Examination, Serum IgE	Follow up 1 week after treatment
Duration of Treatment	1months	Post treatment follow up

Table 2: Test and control drug content

Diseases	Test Drugs	Test Drugs Formulation	Control Drugs
Atopic Dermatitis	Dermovix ointment	*Rosa demascena* 1gm *Zinc oxide* 2gm *Melia azadirachta* 1gm *Sulfur* 3gm *Terminala chebula* 1gm *Plumbi oxidum* rubrum 2gm	Betnovate-N

Table 3: Patient age distribution and frequency

		Frequency	Frequency of Male	Frequency of Female	Percent	Valid Percent	Cumulative Percent
Valid	2-9	16	11	5	26.7	26.7	26.7
	10-19	14	6	8	23.3	23.3	50
	20-29	13	8	5	21.7	21.7	71.7
	30-39	11	7	4	18.3	18.3	90
	Above 40	6	4	2	10	10	100
	Total	60	36	24	100	100	

Table 4: Comparative data between dermovix ointment and betnovte-N cream (Itching)

Level of Improvement	Improved	Not Improved	p value
Dermovix ointment	23 (762.87%)	9 (28.13%)	0.000
Betnovate-N cream	16 (57.14%)	12 (42.86%)	

Table 5: Comparative data between dermovix ointment and betnovate-N cream (Pruritis)

Level of Improved	Improved	Not Improved	p value
Dermovix ointment	19 (63.33%)	11 (36.67%)	0.000
Betnovate-N cream	17 (56.66%)	13 (43.34%)	

Table 6: Comparative data between dermovix ointment and betnovate-N cream (Rashes)

Level of Improvement	Improved	Not Improved	p value
Dermovix ointment	18 (54.54%)	15 (45.46%)	0.000
Betnovate-N cream	15 (55.55%)	12 (44.45%)	

Table 7: Comparative data between dermovix ointment and betnovate-N cream (Dry skin)

Level of Improvement	Complete Improved	Not Improved	p value
Dermovix ointment	21(67.74%)	10 (32.26)	0.407
Betnovate-N cream	17 (58.62%)	12 (41.38%)	

Table 8: Comparative data between dermovix ointment and betnovate-N cream (Scales)

Level of Improvement	Complete Improved	Not Improved	p value
Dermovix ointment	18 (60%)	12 (40%)	0.000
Betnovate-N cream	16 (53.33%)	14 (46.67%)	

Table 9: Comparative data between Dermovx ointment and Betnovate-N cream (Scratches)

Level of Improvement	Complete Improved	Not Improved	p value
Dermovix ointment	19 (57.57%)	14 (42.43%)	0.054
Betnovate-N cream	16 (59.25%)	11 (40.754)	

Table 10(A): Paired sample t-test before and after treatment on test group

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
Pair 1	Clinical Manifestation - Itching After Treatment in Test Drug	1.633	.669	.122	1.384	1.883	13.379	29	.000
Pair 2	Pruiritis Before Treatment in Test Drug - Pruiritis After Treatment in Test Drug	-1.533	1.074	.196	-1.934	-1.132	-7.818	29	.000
Pair 3	Rashes Before Treatment in Test Drug - Rashes After Treatment in Test Drug	-1.167	.950	.173	-1.521	-.812	-6.727	29	.000
Pair 4	Dry Skin Before Treatment in Test Drug - Dry Skin After Treatment in Test Drug	-.167	1.085	.198	-.572	.239	-.841	29	.407
Pair 5	Scales Before Treatment in Test Drug - Scales After Treatment in Test Drug	1.333	.711	.130	1.068	1.599	10.269	29	.000
Pair 6	Scratches Before Treatment in Test Drug - Scratches After Treatment in Test Drug	1.500	.630	.115	1.265	1.735	13.047	29	.054

STATISTICAL ANALYSIS

All the data obtained from Shifaul-Mulk Memorial Hamdard University Karachi and Al-Rasheed Darushifa Malkani Liaqut Pur was subjected to statistical analysis (SPSS version 18.0) to determine the level of significance of case control study.

RESULTS

Atopic dermatitis is characterized by certain clinical (erythema, scales & vesicles) and histopathological changes. Atopic Dermatitis is most common skin inflammatory disease, which leads to long-term swelling and redness (inflammation) of the skin.

There are different systems of medicine for the atopic dermatitis treatment, such as Allopathic, Homeopathic, Unani, Ayurvedic, Chinese etc. In allopathic therapy, different systemic and topical drugs are used for atopic dermatitis treatments, which are given below

Systemic	Local
Qurs-e-musafeen	Dermovix
Musafeen syrup	Marham kharish jaded
Sharbaat-e-unaab	
Majoon muafi khas	Marham kafoor
Itraifil shatra	Hiknol
Arq-e-shatra	Marham eczema
Arq-e-mundi	Hamdard marham

Conventional treatment is more costly so low socioeconomic patients cannot afford it and these therapies also have different hazards or side effects. Unani system of medicine is a traditional system of medicine having many well-known effective and cost saving treatments for atopic dermatitis without any major side effect. Therefore a natural treatment for atopic dermatitis is given below.

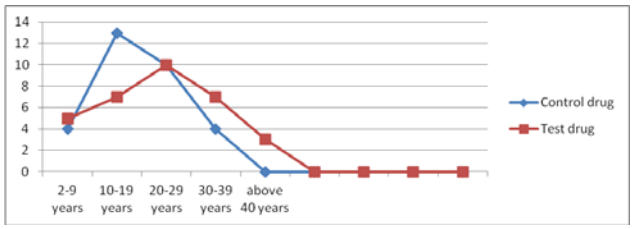
Table 10(B): Paired sample t-test before and after treatment on control group

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Itching Before Treatment in Control Drug - Itching After Treatment in Control Drug	1.600	.724	.132	1.330	1.870	12.105	29	.000
Pair 2	Pruiritis Before Treatment in Control Drug - Pruiritis After Treatment in Control Drug	1.500	.682	.125	1.245	1.755	12.042	29	.000
Pair 3	Rashes Before Treatment in Control Drug - Rashes After Treatment in Control Drug	.933	.740	.135	.657	1.210	6.911	29	.000
Pair 4	Dry Skin Before Treatment in Control Drug - Dry Skin After Treatment in Control Drug	1.533	.860	.157	1.212	1.855	9.761	29	.000
Pair 5	Scales Before Treatment in Control Drug - Scales After Treatment in Control Drug	1.633	.765	.140	1.348	1.919	11.696	29	.000
Pair 6	Scratches Before Treatment in Control Drug - Scratches After Treatment in Control Drug	1.700	.915	.167	1.358	2.042	10.172	29	.000

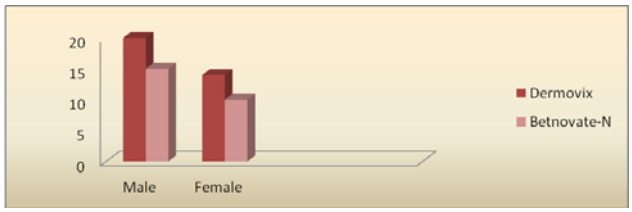
Herbal/Unani treatment

A review literature of ingredients of eastern coded formulation Dermovix and used control allopathic medicines are documented earlier. One of the major objectives of this study is to correlate the effects of both drugs (control and test) on atopic dermatitis. This study was carried out on 60 patients after taking written consent from them at different health care Shifa-ul-Mulk Memorial-Hospital, Faculty of Eastern Medicine, Hamdard University and Al-Rasheed Darulshifa Malkani Liaqut Pur. All the patients included in this study were selected according to inclusion criteria. The patients were divided into 2 groups *i.e.* control and test group on whom allopathic and eastern formulations were applied respectively. The patients suffering from any other skin disease, diabetes, hypertension, renal diseases, severe psychiatric disorders, hepatitis and any type of immuno-compromised patients *i.e.* HIV were excluded from the study and pregnant women excluded. The clinical trial proforma was filled with detailed history, signs, symptoms and prognosis on each follow up visit under the supervision of monitor physician and supervisor. The study is prospective case control clinical trials and the variables are divided into dependent and independent

groups *i. e.* control and test drugs are independent variables while sign and symptoms, level of improvement are dependent variables. The patients who were sustained the inclusion criteria were selected for this research project. A patient questionnaire also serves as a data sheet having documented with the subjects at entry that record the information concerning the sex and age of the subjects, clinically. Normal and Numerical Data: The variables are divided into different categories like total numbers of patients are distribution of individual signs and symptoms and level of improvement of all test and controlled medicines.



Graph 1: Patient age distribution and frequency



Graph 2: Ratio of males and females

The purpose of the present investigation was to compare the eastern/herbal medicine with allopathic medicine so as to assess its ultimate effects for its curative function. Controlled studies include a group given a comparison treatment of allopathic to one group and the second group traditional medicine to establish effectiveness and safety by standard parameters. As such the constituents of dosage form design of coded Dermovix Ointment as reported on the formulation exert therapeutic activity; therefore, this study has been compared with standard therapy such as Betnovate-N cream.

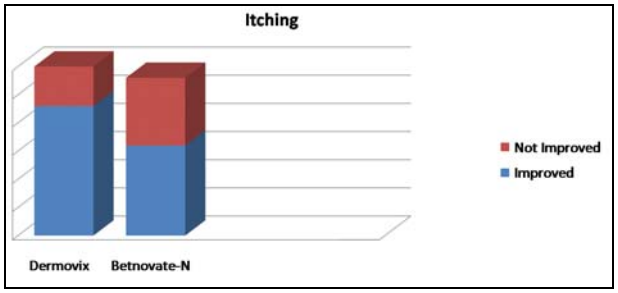


Fig. 1: Improvements in itching

The patients were registered from the general O.P.D and hospitalized to the clinical research ward of the hospital. This study trial was supervised by the Ethical Committee of the Hamdard University. Safety of the subject in clinical trial based on atopic dermatitis was derived from the earlier studies on atopic dermatitis. Multiple primary variables in the sign and symptoms were quite sufficient to cover the range effect of the therapy. Applying the designed format collected the data out of 60 patients, 30 patients were given herbal coded Dermovix ointment and 30 patients were treated with Betnovate-N cream. The parameters that were taken in signs and symptoms for AD were itching, pruritis, rash, papules, dry skin, scales, scratches, eczema etc.

The aim of this study was to evaluate efficacy and safety of these herbal preparations for treating AD. The therapeutic evaluation of this therapy were conducted on 60 patients clinically, diagnosed cases of AD at Shifaul-Mulk Memorial-Hospital, Hamdard University, Al-Rasheed Darushifa Malkani Liaqut Pur. From general OPD the patients were registered and hospitalized. Generally the cases established the supportive treatment in the form of complete rest and by giving diet free from allergens. The age distribution of patients classified into the different class intervals ranging the age starting from 2 to above 40 years. The age distribution of 60 patients that was recorded having 5 class intervals i.e. 2-9, 10-19, 20-29, 30-39 and above 40 shown in table 3. The enrolled patients between 2-9 years of age only were only 16 patients and 14 patients were in class interval between "10-19" and between ages of "20-29" class interval 13 patients were registered. 11 patients were among the class interval 30-39. Above 40 year of age the total numbers of patients were 6.

Patients' characteristic

Itching, pruiritis, dry skin, rash, papules, scales, scratches were the parameters taken in signs and symptoms for atopic dermatitis. Among these, 23 patient shaving complaints of itching, 21 patients complaints with pruiritis, 19 patients complain of dry skin were recorded, while 15 patients with rash were registered, again 15 patients with papules, 13 patients of scales, 11 patients with scratches were registered. The therapeutic evaluation was made on basis of improvement in the subjective signs and symptoms, and clinical observations and follow up intervals during treatment.

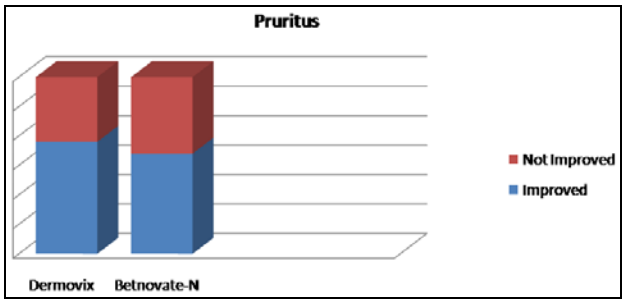


Fig. 2: Improvements in pruiritis.

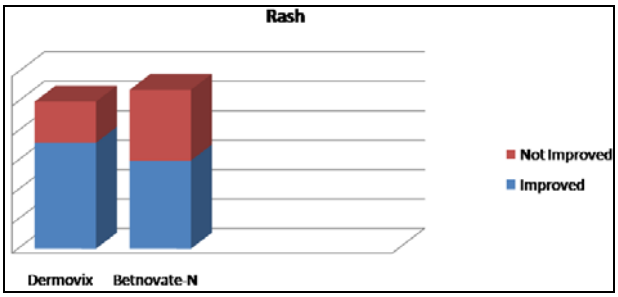


Fig. 3: Improvements in rash

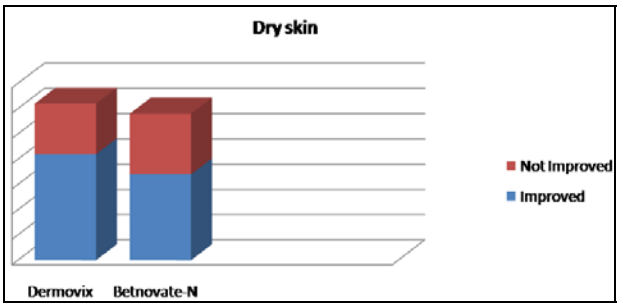


Fig. 4: Improvement in dry skin

Clinical response

Restricted diet was given to the hospitalized and physical examination was carried out before, during and after treatment. The therapeutic evaluation of the drug was made on the basis of improvement in the subjective signs and symptoms, clinical assessment, at periodic intervals during the course of treatment

Itching

Itching complains has been recorded in both test and control group patients. Patients presenting with complaint of itching observed improvement in 54% of patients and 46% of patient did not improve with Dermovix ointment. The effects of Betnovate-N cream only 48% of the patient indicated complete improvement as compared 52% patients showed no improvement. The overall effects of Dermovix ointment were better than Betnovate-N cream as shown in table 4 and fig. 1.

Pruiritis

Pruiritis completely improved in 49% of the patient and not improved in 51% of the patients treated with Dermovix ointment. By Betnovate-N cream the improvement in 41% of the patient and no improvement in 59%. Overall comparative result of the data showed that eastern/herbal formulation Dermovix ointment were more effective and compliance rate is much better than Betnovate-N cream as shown in table 5 and fig. 2

Rashes

It is the most common complaint in-patient suffering from atopic dermatitis. Presented with the complaint of rash showed that the Dermovix ointment was effective in 48% of the patient and not effective in 52%. While in case of control drug only 41% of the patients had shown complete improvement and 59% show no effect. It indicates that test drug has shown better response than control drug as shown in table 6 and fig. 3.

Dry skin

It was observed that test drug was effective in about 58% of cases and 42% of the cases showed ineffective whereas control drug had shown 36% of complete improvement and 64% of the patient had shown failure rate. It had described that test drug is more effective than control drug as shown in table 7 and fig. 4.

Scales

In case of this complaint it was observed that test drug had shown 65% of patients completely improved and 35% of patients that had shown no satisfactory response to the treatment. In case of control drug 55% of the patients had observed to show complete improvement and 45% patients were noticed that had shown no effect. By this comparison it had clearly observed that test drug had shown better clinical response than control as shown in table 8 and fig. 5.

Scratches

In case of this complaint it was observed that test drug had shown 68% of patients completely improved and 32% of patients that had shown no satisfactory response to the treatment. In case of control drug 52% of the patients had observed to show complete improvement and 48% patients were noticed that had shown no effect. By this comparison it had clearly observed that test drug had shown better clinical response than control as shown in table 9 and fig. 6

Summary

Overall results of individual group are given in table 10 by using Paired sample t-test and level of significance of all the symptoms is calculated. Generally all the prescribed medicines has shown efficacy equal to each other. When we compare all these effects and patient's complaints then *Test group* have shown better results because of no side effects.

DISCUSSION

It is reported that this it belongs to most prevalent skin diseases both in children and infants. It is reported that most of the parents prefer to use non-steroidal therapy for the treatment of symptoms associated with AD to their children (Hon *et al*., 2006; Kojima *et al*., 2013). It is recommended to locally apply emollient therapy according to current guidelines to treat AD, whereas it has main been common that to control flare-ups and to get immediate relief corticosteroids are very often used (Eichenfield *et al*., 2014; Hanifin *et al*., 2004; Ring et al., 2012). Mostly the parents are reluctant to use topical

steroid because the children do not complete their prescribed time duration for their treatment (Hon *et al*., 2006; Kojima *et al*., 2013). Therefore, there is need of herbal coded topical skin cream that is safe and effective to treat this disorder. It has been observed that herbal coded Dermovix proven as well tolerated and has shown better efficacy without any side effects. None of the patient discontinued the clinical trials due to any of adverse events or for any other reason. Recent studies conducted on adults also proven that these type of products can potentially improve the skin barrier and symptoms associated with AD, as evidenced using body cream and by decrease in TEWL as well but exert some side effects on prolong use and their efficacy were proven in specific age groups (Weber *et al*., 2014). Dermovix ointment has proven its efficacy in age group 2 years to patients above than 40 years. Although it is not studied in infant and younger children but this product may provide an effective herbal treatment for AD in all age groups. It is recommended to conduct large scale clinical trial in future to use this product to large number of patients in terms to prove its efficacy more authentic way.

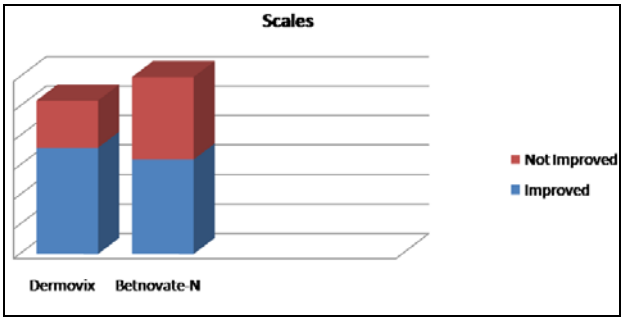


Fig. 5: Improvements in scales

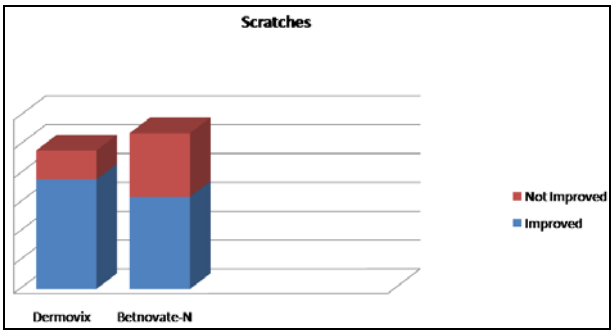


Fig. 6: Improvements in scratches

REFERENCES

Barbeau M and Bpharm HL (2006). Burden of atopic dermatitis in Canada. *Int. J. Dermatol*., **45**: 31-36.

Ben Gashir MA, Seed PT and Hay RJ (2004). Quality of life and disease severity are correlated in children with atopic dermatitis. *Br. J. Dermatol*., **150**: 284-90.

Bieber T (2008). Atopic dermatitis. *N. Engl. J. Med*., **358**: 1483-1494.

Boguniewicz M and Leung DY (2010). Recent insights into atopic dermatitis and implications for management of infectious complications. J. *Allergy Clin. Immunol.*, **125**: 4-13.

Carlsten C, Dimich-Ward H, Ferguson A, Watson W, Rousseau R and Dybuncio A (2013). Atopic dermatitis in a high-risk cohort: Natural history, associated allergic outcomes and risk factors. *Ann. Allergy Asthma Immunol*., **110**(1): 24-8.

Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger, K……, Sidbury R (2014). Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J. Am. Acad. Dermatol*., **71(1)**: 116-132.

Gu H, Chen XS, Chen K, Yan Y, Jing H, Chen XQ, Shao CG and Ye GY (2001). Evaluation of diagnostic criteria for atopic dermatitis: Validity of the criteria of Williams *et al*. in a hospital-based setting. *Br. J. Dermatol*., **145**: 428-33.

Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, I Van Voorhees AS (2004). Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association ‘‘Administrative Regulations for Evidence-Based Clinical Practice Guidelines.’’ *J. Am. Acad. Dermatol*., **50(3)**: 391-404.

Hon KL, Kam WY, Leung TF, Lam MC, Wong KY, Lee KC, I Ng PC (2006). Steroid fears in children with eczema. *Acta. Paediatrica*., **95**: 1451-1455.

Krakowski AC, Eichenfield LF and Dohil MA (2008). Management of atopic dermatitis in the pediatric population. *Pediatrics*, **122**: 812-824.

Kojima R, Fujiwara T, Matsuda A, Narita M, Matsubara O, Nonoyama S, I Matsumoto K (2013). Factors associated with steroid phobia in caregivers of children with atopic dermatitis. *Pediatr. Dermatol.*, **30(1)**: 29-35.

Lawson V, Lewis-Jones MS, Finlay AY, Reid P and Owens RG (1998). The family impact of childhood atopic dermatitis: The dermatitis family impact Questionnaire. *Br. J. Dermatol*., **138**: 107-113.

McKenna SP and Doward LC (2008). Quality of life of children with atopic dermatitis and their families. *Curr. Opin. Allergy Clin. Immunol.*, **8**: 228-231.

O'Connell EJ (2004). The burden of atopy and asthma in children. *Allergy*, **59**(Suppl 78): 7-11.

Olesen AB, Ellingsen AR, Olesen H, Juul S and Thestrup-Pedersen K (1997). Atopic dermatitis and birth factors: Historical follow up by record linkage. *BMJ*., **314**: 1003-1008.

Schultz LF and Hanifin JM (1992). Secular change in the occurrence of atopic dermatitis. *Acta. Derm. Venereol. Suppl. (Stockh)*, **176**: 7-12.

Spergel JM (2010). From atopic dermatitis to asthma: The atopic march. *Ann. Allergy Asthma Immunol*., **105**(2): 99-106.

Spergel JM and Paller AS (2003). Atopic dermatitis and the atopic march. *J. Allergy Clin. Immunol*., **112**: S128-139.

Strachan DP (1989). Hay fever, hygiene and household size. *BMJ*., **299**: 1259-1260.

Svensson A, Edman B and Moller H (1985). A diagnostic tool for atopic dermatitis based on clinical criteria. *Acta. Derm. Venereol. Suppl. (Stockh).*, **114**: 33-40.

von Mutius E, Weiland SK, Fritzsch C, Duhme H and Keil U (1998). Increasing prevalence of hay fever and atopy among children in Leipzig. *East Germany Lancet.*, **351**: 862-826.

Weber TM, Babcock MJ, Herndon JHJr, Schoelermann AM, Filbry A, Scherdin U, I Rippke F (2014). Steroid-free emollient formulation reduces symptoms of eczema and improves quality of life. *J. Drugs Dermatol*., **13(5)**: 589-595.

Weinmann S, Kamtsiuris P, Henke KD, Wickman M, Jenner A and Wahn U (2003). The costs of atopy and asthma in children: Assessment of direct costs and their determinants in a birth cohort. *Pediatr Allergy Immunol*., **14**: 18-26.

Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R, Asher I, Beasley R, Björkstén B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Shah J, Sibbald B, Strachan D, von Mutius E and Weiland SK (1999). Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J. Allergy Clin. Immunol*., **103**: 125-38.