Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:905-912.

Original Article

A double-blind randomized controlled trial assessing the efficacy of topical steroids alone and combined with tacrolimus for the treatment of chronic hand eczema

Hina Khoso[1], Muhammad Fahim[2]

[1]Department of Dermatology, Shaheed Mohtarama Benazir Bhutto Medical University, Larkana, Sindh.
[2]Tehsil Headquarters Hospital Takhtbhai, Mardan.

Abstract

Objective To assess the effectiveness of topical tacrolimus combined with topical super potent steroids to treat Chronic Hand Eczema (CHE).

Methods This study had one hundred and twenty patients in total, divided into two groups. Patients in Group A were treated with topical clobetasol 0.05% while Group B received same strength of clobetasol combined with 0.1% tacrolimus. Using Physician Global Assessment (PGA), Dermatology Quality of Life Index (DLQI), and Hand Eczema Severity Index (HECSI), disease severity was evaluated at baseline and then on a monthly basis. Final Assessment done after 6 months.

Results In Group A, the female to male ratio was 1.4 compared to 1.8 in Group B. In Groups A and B, the duration of disease was 5.6±2.7 years and 6.1±3.4 years, respectively. The two groups' disease severity at baseline was comparable. Patients in Group B showed better signs and symptoms improvement than those in Group A after 6 months, which was correlated with higher decreases in HESCI, DLQI, and PGA scores, respectively (p value <0.05).

Conclusion Our study showed that the treatment of CHE was more effective when topical tacrolimus was combined with super potent steroids.

Key words
Clobetasol; Chronic Hand Eczema; DLQI; HESCI; PGA; Tacrolimus.

Introduction

Chronic hand eczema is an inflammatory skin disease mostly involving the hands. It is a common disorder with an estimated annual frequency of 10 to 14%, with the majority of cases reported being in females.[1] Additionally, the most prevalent occupational disease worldwide.[2] CHE is defined as eczematous lesions on one or both hands that lasts more than six months or recurs more than twice yearly.[3] Redness, scaling, thickening, hyperkeratosis, and fissuring are typical characteristic features. Pruritus is an invariable feature with varying degree of intensities. Finger, palms, and forearm are the areas of involvement in decreasing order of frequency. Sometimes feet may be affected at the same time.[4] The etiopathogenesis of disease is influenced by a number of factors, including genetic, hormonal, and occupational and

Manuscript Received on: August 30, 2023
Accepted on: February 07, 2024
Address for correspondence
Dr. Muhammad Fahim
Consultant Dermatologist,
Tehsil Headquarters Hospital Takhtbhai, Mardan.
Email: khandermatologist2021@gmail.com

environmental. Housework, cement work, hair styling, farming, health care profession, and labor work are among the occupations where chronic hand eczema is frequently reported. Regardless of occupation, repeatedly exposing hands to wet work is the main aggravating factor.[5] History of atopy is found in 20–30% of patients in addition to various symptoms in other body regions such urticaria, conjunctivitis, and rhinitis.[6]

A significant quality of life impairment is linked to chronic hand eczema, which can lead to discomfort, pain, functional restrictions, and Occupational challenges. Besides physical morbidities, Other psychologic issues like sleep difficulties, anxiety, social phobia, and depression are also found in such patients.[7] It also prevents patients from engaging in specific activities and is associated with stigma due to its presence in such visible body parts.

The Physician Global assessment (PGA), Eczema Severity Index (HSECI), Dermatology Quality of Life Index (DLQI), Osnabrück Hand Eczema Severity Index (OHSI), and Clinical Photo Guide (CPG) are a few of the objective and subjective evaluation techniques available to determine the severity of chronic hand eczema.[8] We chose two objective (HESCI&PGA) and one subjective (DQLI) tool for our investigation. The objective diagnostic tool known as HECSI is frequently used to evaluate morphological signs such as redness, infiltration, fluid filled vesicles, fissures, scaling, and edema. Each hand is divided into five areas: Fingertips, fingers (other than the tips), palms, backs of hands, and wrists. The severity of the aforementioned symptoms is rated for each of these locations as follows: 0-no skin changes; 1-mild disease; 2-moderate; and 3-severe. Both hands' areas of involvement receive a score of 0: 0%; 1: 1-25%; 2: 26-50%; 3: 51-75%; and 4: 76-100%. Finally, a maximum score of 360 can be obtained by multiplying the area score by the sum of the intensities of all clinical features.[9] PGA is another objective assessment toll used to measure disease severity not only for hand eczema but other dermatologic diseases as well. It is graded as sever, moderate, mild, almost clear and clear. The Dermatology Life Quality Index (DLQI) measures six aspects of daily life experienced over the course of the previous week. It is a subjective tool and is scored on a 10-item questionnaire based on the main headings: (i) symptoms and feelings, (ii) daily life activities, (iii) leisure/ recreation items, (iv) work and school, (v) personal /family relationship and (vi) treatment. Each question's score is added up to determine the DLQI score, which has a maximum score of 30 and a minimum score of 0.[10]

Chronic hand eczema management is challenging and frequently necessitates a multimodal strategy that incorporates medicinal therapies and dietary changes.[11] To relieve symptoms, reduce inflammation, and preserve the integrity of the skin barrier, topical therapies such moisturizers, emollients, and corticosteroids are frequently used. Identifying and avoiding triggers and irritants that might make the problem worse, such as soaps, detergents, and allergens, is equally important. Taking preventive precautions, such as wearing gloves and applying barrier creams, can add another line of defense against allergens and irritants. The natural moisture balance of the skin can be preserved by maintaining a regular skincare routine including gentle cleansing, moisturizing, and avoiding excessive water/ irritant use.[12]

In severe cases phototherapy, systemic medicines, or targeted therapies may be recommended. Despite the fact that there are numerous therapeutic alternatives, topical potent steroids and emollients remain the mainstay of

treatment, especially in resource poor countries.[13] Topical steroids, however, are linked to a wide range of side effects, including atrophy, telangiectasia, Pituitary axis suppression, infections, rebound eczema flare-up, contact sensitization, irritant contact dermatitis, poor wound healing, tachyphylaxis, hypertrichosis, bruising and dyspigmentation.[14] Looking at these adverse effects, it is vital to evaluate other topical drugs with better tolerability The new family of medications known as calcineurin inhibitors (tacrolimus) is successfully treating a variety of inflammatory dermatoses. Similar to cyclosporin, it prevents the production of interleukin-2, which is crucial for T cell activation and proliferation resulting in reduction of inflammation.[15] There is limited data available on the role of calcineurin inhibitors in the treatment of CHE thus this study attempted to fill this research gap.

Methods

A total of one hundred and twenty patients (60 in each group) participated in the randomized control trial. Sample size was calculated using G power software, keeping confidence interval and power of the test at 95% & 80 respectively. After getting permission from the hospital administration, patients were randomization into two groups using lottery method. After obtaining the institutional permission no. 145/THQ dated February 01, 223; all patients provided written consent after being fully informed of the study's duration, methodology, potential side effects of drugs, and other complications. Using fingertip unit, Patients in Group A applied only clobetasol cream (0.05%) while those in Group B were treated with topical tacrolimus cream (0.1%) in addition to clobetasol cream (0.05%). All patients took a twice-daily dose for the first two weeks followed by switching to a twice-weekly regimen for the remaining 22 weeks. All patients were advised to take the aforementioned medications in addition to using regular moisturizers and taking preventative measures including wearing gloves during occupational exposure. DLQI and HECSI were the primary outcomes while PGA was the secondary one.

Inclusion criteria All male and female patients between the age 18- 55 with hand lesions suggestive of CHE and severity scores other than clear and almost clear on the physician global assessment (PGA), were included in the study after providing written consent.

Exclusion criteria Patients who refused to give their consent to participate in the study, refused to adopt safer daily habits like avoiding wet work, solvents, and detergents, or who refused to wear vinyl gloves, or who had received treatment with phototherapy (UVB), X-ray radiation, systemic corticosteroids, retinoids, or immunosuppressant medications within the last four weeks, were excluded from the study. Other CHE mimics such as psoriasis, lichen planus, and tinea manum were also excluded.

SPSS 25 was used to put and analyze the data. . Age and disease duration were computed as mean±SD. At baseline and six months following therapy, the DLQI, PGA, and HECSI scores were calculated. Frequencies and percentages for gender, history of atopy and efficacy were determined. A chi-square test was performed to assess the efficacy of understudy drugs in the two groups, with a two-sided P-value of <0.05 being considered significant. Age, gender, disease duration, and DLQI, HECSI, and PGA scores were compared between the two groups. A two-sided chi-square test was used for stratification in order to determine the effect of these variables on the result. The proportion of patients reverting to clear/almost clear in PGA scoring system and the decrease in the DLQI and HECSI scores relative to baseline were used to measure effectiveness.

Results

A total of 120 patients took part in this trial. **Table 1** displays the basic demographic and clinical data of all participants. With 58.33% of patients in Group A and 65% of patients in Group B, overall female patients made up the majority in both groups. At the Baseline, age, occupation, duration and severity of Disease were similar between the two groups. In Group A and Group B, the mean DLQI and HECSI, were 13.4±5.2 and 38.6±117.11 respectively.

The PGA score indicated that 76.6% of patients in Group B and 83.3% of patients in group A fell into the moderate/severe disease. Based on the two subjective assessment tools clinical improvement were seen in both groups but was more significant in Group B patients (P values=0.0001 and 0.0079 for DLQI and HECSI respectively) (**Figure 1)**. On the basis of the PGA grading system, a greater proportion of patients in Group B reverted to the clear/almost clear categories (p value=0.0069) (**Figure 2)**. Among various factors, female gender in both groups was linked to refractory disease, which may have resulted from repeated exposure to detergents and a lack of adaptation of protective measures such as wearing vinyl gloves.

Discussion

CHE is a long-lasting condition that affects the hands preferentially and causes, itching, pain and discomfort. Recurrent flare-ups are a defining feature and it can have a substantial effect on everyday activities and quality of life.

Effective management of this persistent dermatological problem requires an understanding of the causes, symptoms, and available treatments for CHE. Emollients, topical and systemic steroids, calcineurin inhibitors, topical vitamin D analogues, UVB, systemic immunosuppressive medication and other dietary and lifestyle changes are common management strategies. The aim of this study was to evaluate the combined efficacy topical steroids and calcineurin inhibitors in the treatment of CHE.

Table 1 Basic clinical and demographic data of study participants.

Parameter	*Group A*		*Group B*		*P value*
Number of patients	60		60		
Male	25		21		
Female	35		39		
Disease duration (years)	5.6±2.7		6.1±3.4		0.3742
Age (years)	38.2±12.33		35.9±11.47		0.2922
Occupation					
House wife	16		17		
House maid	7		5		
Farmer	13		11		
Laborer	4		6		
Industry worker	5		3		
Mason	6		8		
Health Care professional	4		2		
Hair dresser	2		4		
Others	-		-		
Unemployed	5		4		
History of atopy	14%		17%		
HESCI score	Baseline	At 6 months	Baseline	At 6 months	
	38.61±17.11	22.9±9.5	40.20±14.22	18.5±8.3	0.0079
DQLI	Baseline	At 6 months	Baseline	At 6 months	
	13.4±5.2	10.4±4.7	11.8±4.8	7.3±3.9	0.0001

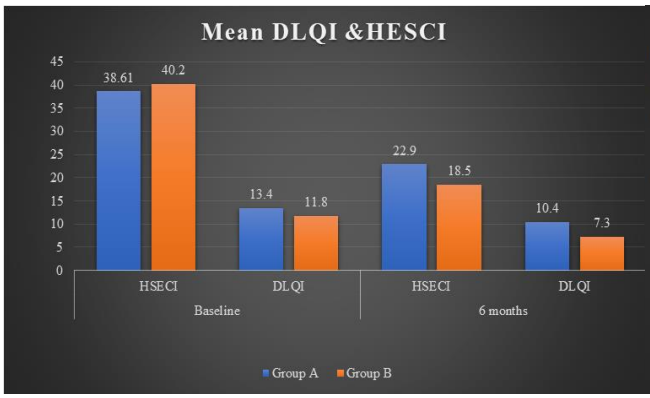

Figure 1 DLQI and HECSI at baseline and 6 months.

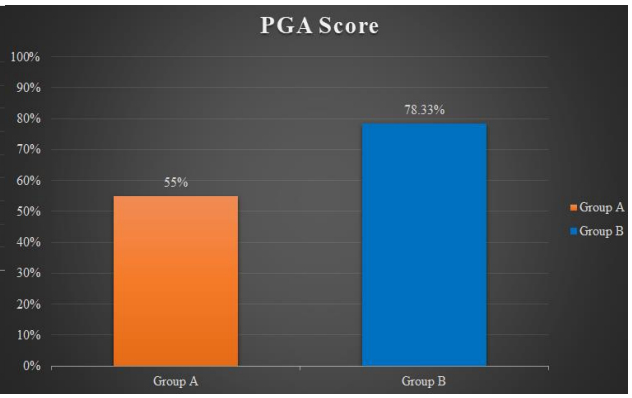

Figure 2 Percentage of patients reverting to clear/ almost clear categories after 6 months.

There were total 120 patients in our trial, 60 in each group. Both groups had a similar basic clinical profile, with a female constituting the majority of patients. For a period of six months, Group A used clobetasol 0.05% ointment alone, whereas the patients in Group B applied clobetasol in combination with tacrolimus 0.1% on their hands. The combination group showed greater clinical improvement as seen by lower DLQI and HECSI scores (p values=0.0001 and 0.0079, respectively).

A cross-sectional study carried out in India assessed the severity of hand eczema and quality of life. In total, 109 patients participated in the trial. The average age, length of the illness, and gender profile were similar to those in our study. HECSI and DQLI scores were 48.81±27.92 and 9.14±5.20, respectively, and these two assessment methods had a strong association. Similar to our study, repeated exposure to detergents was the primary aggravating factor, which is why eczema severity was slightly greater in female patients as indicated by DLQI.[16]

In order to treat chronic hand eczema, Leon H. Kircik *et al*. evaluated the efficacy of 0.05 percent clobetasol in an emulsion formulation. The study included 30 patients. For two weeks, each patient administered the emulsion mixture twice daily. The investigator static global assessment (ISGA) scoring system was used to determine efficacy. At final assessment the ISGA score, which was used to determine therapy success, improved by at least one grade in 96.7% of patients.[17]

Uma Shankar Agarwal *et al*. assessed the effectiveness of oral azathioprine and clobetasol 0.05% in a randomized control trial. The trial involved 108 individuals, with one group applied clobetasol ointment twice a day and the other used it in conjunction with oral azathioprine 50mg once a day on a regular basis for six months. Statistics were comparable to our study in terms of mean age and disease duration. Male patients were more prevalent in both categories, which may be explained by larger number of labor participants enrolled in this study. At the final evaluation, the combination group's reduction in the HECSI and itching scores was larger (p values of 0.001 and 0.003, respectively).[18]

Another double-blinded trial evaluated the effectiveness of topical clobetasol cream 0.05% and zinc sulphate cream 2.5% concentration. Similar to our study, the ratio of women to men was higher than 1. For two weeks, 47 patients used clobetasol alone on one hand and a combined formulation on the other. Results demonstrated that the combination group had a decreased recurrence rate on long-term follow-

up as well as significant improvement in clinical parameters (redness, scaling, lichenification, and pruritus) (p value <0.05).[19]

In order to treat CHE, Tasnuva Ashraf *et al*. compared clobetasol ointment and intralesional triamcinolone. Sixty patients took part in the trial, and their age range and gender distribution were similar to those in our study. Patients in Group A applied 0.05% clobetasol ointment twice daily for three months while those in the Group A received treatment with 0.1 ml of 40mg/ml triamcinolone repeated at intervals of 28 days. On follow-up, the HECSI score gradually decreased on both sides, but Group A's decrease was more pronounced (p value=0.001). Patients in the clobetasol group experienced more unpleasant effects, however these effects were not statistically significant (p value >0.05).[20]

Alexandra Katsarou *et al*. compared the efficacy of tacrolimus 0.1% ointment to potent steroid. Thirty patients who had positive reactions to several contact allergens took part in the trial. Patients received either Mometason furoate ointment 0.1% or tacrolimus ointment 0.1% twice daily. Although There was no intergroup variation in terms of efficacy at the final assessment (p value >0.05), clinical parameters (erythema, infiltration, vesiculation, desquamation, presence of cracks, and itching) were dramatically improved in both groups compared to baseline (P value<0.05).[21]

In a study by Jennifer Krejci-Manwaring *et al*. systemic steroids were combined with tacrolimus to determine its efficacy. Thirty-two patients received a Prednisolone for three weeks in tapering manner, with one group administering tacrolimus ointment 0.1% twice daily for 12 weeks on the hands while the other group used its vehicle. Patients in the former group significantly improved in both subjective objective clinical parameters when compared to the vehicle (p <0.05).[22]

Min Yang reported three cases of refractory CHE. All of the patients used different drugs, including topical steroids with high potency, but no discernible improvement was noticed. For initial few weeks, all three patients applied the calcipotriol and betamethasone ointment combination twice daily at first and then once daily. All patients experienced subjective and objective clinical improvement when compared to baseline (p value <0.05). On long-term follow-up, no recurrence was noted. Another study revealed similar efficacy of calcipotriol to potent topical steroid (desoximetason) to treat CHE.[23]

Conclusion

Chronic Hand Eczema is a prevalent condition leading to physical and psychosocial debility. A variety of treatment options are available showing variable efficacy in different patients. We combined topical tacrolimus with Clobetasol ointment and it is concluded that regardless of the underlying cause, tacrolimus combined with super potent steroids give better results than steroids alone in the treatment of chronic hand eczema.

Limitations of the study The application of the study's findings to a larger population may be constrained by the smaller sample size. More significantly, long-term follow-up, which was not done in this trial, is required to determine the long-term effects of the understudied medications on disease progression, remission, and relapse.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest The authors affirm that they have no conflicts of interest to disclose.

Author's contribution

MF: Substantial contribution to study design, critical review, has given final approval of the version to be published.

HK: Substantial contribution to study design, data collection and analysis, manuscript writing, has given final approval of the version to be published.

References

1. Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. *Br J Dermatol*. 2008;**158(4)**:773-7.
2. Armstrong A, Hahn-Pedersen J, Bartlett C, Glanville J, Thyssen JP. Economic burden of chronic hand eczema: a review. *Am J Clin Dermatol*. 2022;**23(3)**:287-300.
3. Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population–a systematic review and meta-analysis. *Contact Dermatitis*. 2021;**84(6)**:361-74.
4. Sehgal VN, Srivastava G, Aggarwal AK, Sharma AD. Hand dermatitis/eczema: current management strategy. *J Dermatol*. 2010;**37(7)**:593-610.
5. Behroozy A, Keegel TG. Wet-work exposure: a main risk factor for occupational hand dermatitis. *Saf Health Work*. 2014;5**(4)**:175-80.
6. Ibler KS, Jemec GB, Flyvholm MA, Diepgen TL, Jensen A, Agner T. Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. *Contact Dermatitis*. 2012;**67(4)**:200-7.
7. Boehm D, Schmid-Ott G, Finkeldey F, John SM, Dwinger C, Werfel T, Diepgen TL, Breuer K. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis*. 2012;**67(4)**:184-92.
8. Duman N, Uzunali E. Clinical assessment of the severity of chronic hand eczema: correlations between six assessment methods. *European Research Journal*. 2015;**1(2)**:44-9.
9. Oosterhaven JA, Schuttelaar ML. Testing the Hand Eczema Severity Index. *Br J Dermatol*. 2020;**182(4)**:e144.
10. Poór AK, Brodszky V, Péntek M, Gulácsi L, Ruzsa G, Hidvégi B, *et al*. Is the DLQI appropriate for medical decision-making in psoriasis patients? *Arch Dermatol Res*. 2018;**310**:47-55.
11. Salvador JS, Mendaza FH, Garcés MH, Palacios-Martínez D, Camacho RS, Sanz RS, González AA, Giménez-Arnau AM. Guidelines for the diagnosis, treatment, and prevention of hand eczema. *Actas Dermo-Sifiliográficas (English Edition)*. 2020;**111(1)**:26-40.
12. Jindal R, Pandhi D. Hand hygiene practices and risk and prevention of hand eczema during the COVID-19 pandemic. *Indian Dermatol Online J*. 2020;**11(4)**:540.
13. Cheng J, Facheris P, Ungar B, Guttman-Yassky E. Current emerging and investigational drugs for the treatment of chronic hand eczema. Expert Opin Investig Drugs. 2022;**31(8)**:843-53.
14. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatol Online J*. 2014;5**(4)**:416.
15. Yoshino T, Nakase H, Honzawa Y, Matsumura K, Yamamoto S, Takeda Y, Ueno S, Uza N, Masuda S, Inui K, Chiba T. Immunosuppressive effects of tacrolimus on macrophages ameliorate experimental colitis. *Inflamm Bowel Dis*. 2010;**16(12)**:2022-33.
16. Varma R, Devi K, Asokan N. A cross-sectional analysis on hand eczema: Severity and quality of life. *Indian Dermatol Online J*. 2021;**12(6)**:952.
17. Kircik LH, Tropmann C. Treatment of mild-to-moderate chronic hand dermatitis with clobetasol propionate 0.05% EF foam: results from an open-label study. *J Drugs Dermatol.* 2011;**10(12)**:1398-402.
18. Agarwal US, Besarwal RK. Topical clobetasol propionate 0.05% cream alone and in combination with azathioprine in patients with chronic hand eczema: an observer blinded randomized comparative trial. *Indian J Dermatol, Venereol Leprol*. 2013;**79**:101.
19. Faghihi G, Iraji F, Shahingohar A, Saidat AH. The efficacy of '0.05% clobetasol+ 2.5% zinc sulphate'cream vs.'0.05% clobetasol alone'cream in the treatment of the chronic hand eczema: a double-blind study. *J Eur Acad Dermatol Venereol*. 2008;**22(5)**:531-6.

20. Ashraf T, Paul HK, Sikder MS, Zakaria AS, Bhuiyan SI, Snigdha KS. Efficacy and safety of intralesional triamcinolone acetonide in the treatment of chronic hand eczema. *Bangabandhu Sheikh Mujib Medical University Journal*. 2017;**10(3)**:129-31.
21. Katsarou A, Makris M, Papagiannaki K, Lagogianni E, Tagka A, Kalogeromitros D. tacrolimus 0.1% vs mometasone furoate topical treatment in allergic contact hand eczema: a prospective randomized clinical study. *Eur J Dermatol*. 2012;**22(2)**:192-6.
22. Krejci-Manwaring J, McCarty MA, Camacho F, Manuel J, Hartle J, Fleischer Jr A, Feldman SR. Topical tacrolimus 0.1% improves symptoms of hand dermatitis in patients treated with a prednisone taper. *J Drugs Dermatol*. 2008;**7(7)**:643-6.
23. Yang M, Chang JM. Successful treatment of refractory chronic hand eczema with calcipotriol/ betamethasone ointment: A report of three cases. *Exp Ther Med*. 2015;**10(5)**:1943-6.