Journal of Pakistan Association of Dermatologists. 2020; **30(1)**: 3-8.

Original Article

Efficacy and safety of low dose Methotrexate in the treatment of chronic hand eczema

Nandita Ghosh, Tabassum Nasrin, Hasan Mahmud, Harasit Kumar Paul

Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Abstract

Background Hand eczema is often a chronic, multifactorial disease which has enormous socioeconomic consequences and a massive impact on patients' quality of life.

Objective To assess the efficacy and safety of low-dose oral methotrexate in patients of chronic hand eczema.

Materials and Method This randomized controlled trial was carried out in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2013 to January 2014. In this study, we enrolled 66 patients through purposive sampling, out of which 33 patients were enrolled in group-A (Study-group) who were treated with low dose oral methotrexate (MTX) in a dose of 0.1 mg/kg body weight once weekly for three months and 33 patients were in group-B (Control group) who underwent therapy with topical clobetasol propionate (0.05%) 2 times daily for 2 weeks then every alternate day for up to three months. The effects of treatment were evaluated using Hand Eczema Severity Index (HECSI) score at base line and at twelfth week and the side effects were unveiled by history, clinical examination and laboratory investigations.

Results In this study male and female ratio was 1: 1.08. At baseline, mean HECSI score in group-A and group-B were 24.51 (±17.33) vs. 21.50 (±18.40). At 12th week follow up mean HECSI score in group-A 6.00 (±4.93) and that of in group-B was 1.07 (±0.39) which was statistically highly significant ($p<0.0001$). In group-A, mean HECSI scores at baseline and at 12th week follow up were 24.51 (±17.33) and 6.00 (±4.93). The difference was statistically significant ($p<0.05$). In group-B, mean HECSI scores at baseline and at 12th week follow up were 21.50 (±18.40) and 1.07 (±0.39). This difference also was statistically significant ($p<0.05$). Adverse effects were observed only in group-A. About 11.11% patients had gastrointestinal adverse events and 3.73% had increased liver enzyme.

Conclusion Low dose oral Methotrexate (0.1 mg/kg body weight once weekly) is effective and safe but not a better option than topical clobetasol propionate (0.05%) in chronic hand eczema.

Key words
Chronic hand eczema, low dose methotrexate, topical clobetasol propionate.

Introduction

Hand eczema is an inflammatory skin disease characterized in the acute phase by erythema, oedema and sometimes vesicles. In the chronic state the skin changes are dominated by lichenification, scaling and fissures, which may cause pruritus and pain. Severity varies in extent and intensity. There may be a few small patches but in some cases most of the skin on the hands may be affected. Hand eczema results from

Address for correspondence
Prof. Dr. Harasit Kumar Paul,
Department of Dermatology & Venereology,
Bangabandhu Sheikh Mujib Medical University,
Dhaka, Bangladesh.
Email: harasit_paul@yahoo.com

irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis. Common irritants include detergents, gloves and organic solvents. Common allergens include metals (e.g. nickel, chromates), preservatives and latex.[1] Each of the conditions have different etiopathogenesis, triggering and aggravating factors but have a similar final step in the outcome i.e. there is an inflammatory response of the skin to various endogenous and/or exogenous factors.[2] Hand eczema of more than three months duration is chronic hand eczema. There are different treatment options available for patients with chronic hand eczema. All approaches have advantage and disadvantages; and none is appropriate for every patient.[3] Emollients and moisturizers are post-exposure skin products that are advisable on diseased skin; they are the mainstay in the prevention of hand eczema. Topical steroids are the mainstay of the pharmacological treatment of hand eczema. Long term potent steroids are effective but the adverse effects of long term topical corticosteroid (skin atrophy, tachyphylaxis, and adrenal suppression) usage are well-known.[4,5] Methotrexate acts as a folate antagonist and decreases cell proliferation, suppresses inflammatory cell chemotaxis & inhibits monocytic/ macrophage activation and lymphocytic function.[1,6] The role of MTX in treating various type of eczema has already been established by many studies.[7-9] In our study, we aimed at comparing the efficacy and safety of low-dose oral methotrexate and topical clobetasol propionate in the treatment of chronic hand eczema.

Methods

This randomized controlled trial was carried out in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2013 to January 2014. It was conducted as a dissertation and this dissertation was accepted by Bangladesh College of Physicians and Surgeons (No.CPS-712/2015/DSN2015-07-008). Total 66 patients who had clinically and histopathologically diagnosed hand eczema of more than 3 months duration, aged between 18-55 years irrespective of sex, who had not received any systemic or topical treatment in the previous 2 months were enrolled. Purposive sampling technique was followed. Patient with pregnancy, lactation, patients receiving any treatment or those who had received any treatment during last 2 months which might influence the course of disease, including systemic steroids, photochemotherapy, ultraviolet B Phototherapy were excluded from the study. Patients with known diseases like diabetes mellitus, hypertension, ischaemic heart disease, thyroid disorders or any other systemic autoimmune disorder and who had history of methotrexate hypersensitivity were also excluded.

Patients were enrolled into two groups. Each group had equal numbers of patients. Even numbered patients were enrolled in study group (Group-A) and the odd numbered patients in control group (Group-B). In group-A, patients were treated with oral methotrexate at a dose of 0.1 mg/kg body weight once weekly for three months and in group-B, patients were treated with topical clobetasol propionate (0.05%) 2 times daily for 2 weeks then every alternate day for up to three months. The patients were scored using HECSI and were recorded. The effects of treatment were evaluated using HECSI score at base line and at twelfth week.

For HECSI each hand is divided into five areas: Fingertips, fingers (except the tips), palms, back of hands, and wrists. For each of these areas the intensity of erythema, induration, papulation, vesiculation, fissuring, scaling, and edema is graded on the following scale: 0-no skin

changes; 1-mild disease; 2-moderate; and 3-severe. For each location (total of both hands) the affected area is given a score from 0-4 (0: 0%; 1: 1-25%; 2: 26-50%; 3: 51-75%; and 4: 76-100%) for the extent of clinical symptoms. Finally, the score given for the extent at each location is multiplied by the total sum of the intensity of each clinical feature, and the total sum called the HECSI score was calculated, varying from 0 to a maximum severity score of 360.[10]

Histories were taken; clinical examination and laboratory investigations (CBC, S. ALT) were done to unveil side effects.

Data were analyzed using computer with the help of SPSS (Statistical Package for Social Sciences) version 21.0 software package. Qualitative data were expressed by frequency and percentage and quantitative data as mean±SD. The two groups were compared on various demographic factors (age, gender, and occupation), severity of hand eczema and adverse effect. Associations between categorical variables were analyzed by chi-square test (χ^2) and between continuous variable by t-test, Mann-Whitney U test, Wilcoxon signed-rank test and Fisher's Exact Test. Statistical significance was set at p-value <0.05 and the confidence interval at 95% level.

Results

In group-A, 51.9% were female and 48.1% were male. In group-B, 57.7% were female and 42.3% were male. The mean age was 38.48 (±11.53) years 34.35 (±12.84) years in group-A and group-B respectively. Majority of study patients in both groups were in the age group of 31-40 years (33.3% vs. 23.1%). In group-A 51.9% of patients were service holders and 48.1% were housewifes. In group-B 34.6% were housewife followed by 30.8%, 19.2% and 15.4% were student, service holder and business person respectively **(Table 1)**.

Table 1 Distribution of age, sex and occupation of the patients (n=66)

	Group-A (%, n 33)	*Group-B (%, n 33)*
Age (Years)		
≤20	11.1	19.2
21-30	14.8	23.1
31-40	33.3	23.1
41-50	22.2	19.2
>50	18.5	15.4
Mean± SD	38.48± 11.53	34.35± 12.84
Gender		
Female	51.9	57.7
Male	48.1	42.3
Occupation		
Student	0.0	30.8
Service (n=5)	51.9	19.2
Business (n=2)	0.0	15.4
Housewife (n=18)	48.1	34.6

Table 2 HECSI score in both groups before treatment and after treatment in study patients (At base line and at 12th week)

HECSI score	*Type of Respondents*		*p-value between groups*
	Group-A (Mean± SD)	*Group-B (Mean± SD*	
At Baseline	24.51± 17.33	21.50± 18.40	0.265
At 12 weeks FU	6.00± 4.93	1.07± 0.39	<0.0001
p value within group	<0.001	<0.001	

At baseline, mean HECSI score were 24.51±17.33 and 21.50±18.40 in group-A and group-B respectively. On the other hand, at 12th week, in group-B mean value of HECSI score was 1.07±0.39 and that of in group-A was 6.00±4.93. In group-A, mean HECSI scores were 24.51 ±17.33 at baseline and at 12th week6.00±4.93. In group-B, mean HECSI scores were 21.50±18.40 at baseline and at 12th week 1.07±0.39 **(Table 2)**.

Independent sample t test was done between groups and paired t test was done within group to measure the level of significance.

Table 3 HECSI score before and after treatment among male and female patients.

	Groups		*p value between groups*
	Group-A Median (Min-Max)	*Group-B Median (Min-Max)*	
Male			
Base line	20.0 (5.0 – 62.0)	22.0 (3.0-84.0)	0.662
After 12 weeks	6.0 (1.0-15.0)	0.0 (0.0 – 2.0)	0.001
p value in group	0.001	0.001	
Female			
Base line	20.0 (3.0-66.0)	5.0 (0.0 – 34.0)	0.004
After 12 weeks	4.0 (0.0 – 20.0)	0.0 (0.0 – 0.0)	0.001
p value within group	0.003	0.001	

Table 4 Distribution of the respondents by adverse effects in both groups at 12th week

Adverse Effects	*Type of Respondents*		*p value*
	Group A (%)	*Group B (%)*	
Gastrointestinal adverse events	11.11	0.0	0.236
Increased liver enzyme values	3.73	0.0	1.000

Among male patients in group-A, median HECSI scores were 20.0 (5.0-62.0) and 6.0 (1.0-15.0) at baseline and at 12 weeks follow up respectively and in group-B, median HECSI scores were 22.0 (3.0-84.0) and 0 (0-2.0) at baseline and at 12 weeks follow up .The difference was statistically significant ($p<0.05$). Among female patients in group A, median HECSI scores were 20.0 (3.0-66.0) and 4.0 (0.0-20.0) at baseline and at 12 weeks follow up respectively and in group-B, median HECSI scores were 5.0 (0.0-34.0) and 0 (0-0) at baseline and at 12 weeks follow up. The difference was statistically significant ($p<0.05$) and represent sign of improvement in both groups of male and female and no statistical significant difference was found in between male and female patients. At 12th week responses are similar in both male and female **(Table 3)**.

Mann-Whitney U test was done between groups and Wilcoxon signed-rank test was done within group to measure the level of significance.

Only group-A had adverse effects. 11.11% patients had complained of gastrointestinal adverse events and 3.73% had increased liver enzyme values **(Table 4)**.

Fisher's Exact Test was done to measure the level of significance.

Discussion

Eczema is an extremely common skin problem in our society. Among all types of eczema, hand eczema is one of the most frequent skin diseases and has often a chronically relapsing course with a poor prognosis resulting in a high social and economic impact for the individual and the society. The role of MTX in treating chronic hand eczema is now a rising issue in various countries of the world. The present study was designed to assess the efficacy and safety of low-dose oral methotrexate and topical clobetasol propionate in the treatment of chronic hand eczema.

In this study, no statistical significant difference was found in between mean HECSI score in group-A and group-B at baseline and at 12^{th} week of treatment. At 12^{th} week, in group-B mean value of HECSI score was 1.07 (±0.39) and that of in group-A was 6.00 (±4.93) which was statistically significant ($p<0001$). In group-A, mean HECSI scores were 24.51 (±17.33) and 6.00 (±4.93) at baseline and at 12 weeks follow

up. The difference was statistically significant ($p<0.001$). In group-B, mean HECSI scores were 21.50 (±18.40) and at baseline and 1.07 (±0.39) at 12 weeks follow up. The difference was statistically significant ($p<0.001$). In a study by Agarwal et al.[11] found less mean percentage improvement in HECSI score which was 64.66 in topical clobetasol treated group. Schram ME[9] et al reported out of 21 patients, 15% patients in the methotrexate group had an exacerbation of their eczema during the study. In our study none of the patients had an exacerbation during treatment. Here is to mention that Schram ME et al.[12] studied the efficacy of MTX in severe Atopic dermatitis. MTX was able to reduce the severity of disease but it failed to completely resolve the eczema which was also concordant with other studies that assessed the safety and efficacy of oral MTX in adults with moderate-to-severe atopic eczema.[4,13] They found that in all patients, the majority of improvement in disease activity was seen by week 12. In their study disease activity was improved by 52% from baseline (95% confidence interval 45-60%). All these results are consistent with our study findings. Difference of total HECSI score between base line and at 12 weeks within group was statistically significant in both groups **(Table 2)**. We found similar response in male and female patients.

Only group-A had adverse effects. About 11.11% had gastrointestinal adverse events and 3.73% had increased liver enzymes. Group-B had no side effects. Agarwal et al[11] also found a surprising report that topical clobetasol treated group had no side effects requiring reduction of dosage or discontinuation of treatment. Weatherheadet al[4] in a study reported a few side effects by MTX. They found 8.3% of patients withdrew at week 16 of the treatment period due to perceived lack of efficacy and side-effects (nausea and recurrent mild cutaneous herpes simplex infection) and 16.6 % patients developed rises in liver enzymes. None of our patients was withdrawn due to lack of improvement or due to adverse effects. Syed AR et al[2] in a study reported, out of 60 patients who were on treatment with oral low dose methotrexate none developed any side effects and no abnormality were there on clinical & laboratory evaluation; these findings are discordant with our results. In our study in group-A 11.11% had gastrointestinal adverse events and 3.73% had increased liver enzymes. We failed to explain these variations. Further studies with bigger sample size might resolve the issue.

Conclusion

Low dose Methotrexate is an effective and safe treatment option for chronic hand eczema. Clobetasol propionate (0.05%) ointment is more effective then low dose methotrexate. A few tolerable side effects are there with low dose methotrexate.

References

1. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. J Am Acad Dermatol 1999; 40: 612–614.
2. Syed AR, Aman S, Nadeem M, Kazmi AH. The efficacy and safety of oral methotrexate in chronic eczema. J Pak Assoc Dermatol 2009; 19: 220-224.
3. Holden CA, Berth-Jones J. Eczema, lichenification, prurigo and erythroderma. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's Textbook of Dermatology, 7th edn. London: Blackwell Publishing; 2004. p.17.1-55.
4. Weatherhead SC, Wahie S, Reynolds NJ. An open-label, dose-ranging study of methotrexate for moderate-to severe adult atopic eczema. Br J Dermatol 2007; 156: 346-51.
5. Ternowitz T, Herlin T. Neutrophil and monocyte chemotaxis in methotrexate

treated psoriasis patients. Acta Derm Venereol (Stockh) 1985; 120: 23.
6. Breathnach SM, Griffiths CEM, Chalmers RJG, Hay RJ. Systemic therapy. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's Textbook of Dermatology. 7th edn. London: Blackwell Publishing; 2004. p. 72.18-49.
7. Zoller L, Ramon M, Bergman R. Low dose methotrexate therapy is effective in late-onset atopic dermatitis and idiopathic eczema. Isr Med Assoc J 2008 Jun; 10:413-4.
8. A Mittal, A K Khare, Lalit Gupta, Sharad Mehta, Anubhav Garg. Use of Methotrexate in recalcitrant eczema. Indian J Dermatol 2011; 56: 232.
9. Goujon C, Bérard F, Dahel K, Guillot I, Hennino A, Nosbaum A, Saad N, Nicolas JF. Methotrexate for the treatment of adult atopic dermatitis. Eur J Dermatol 2006; 16: 155-8
10. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter and intraobserver reliability. Br J Dermatol 2005; 152: 302-7.
11. 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: 101-3.
12. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol 2011; 128(2): 353-9.
13. Shaffrali FC, Colver GB, Messenger AG, Gawkrodger DJ. Experience with low dose methotrexate for the treatment of eczema in the elderly. J Am Acad Dermatol 2003; 18: 417-9.