Effectiveness, Safety and Tolerability of Methotrexate in Chronic Urticaria: At a Tertiary Care Centre

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ABSTRACT

Introduction: Chronic urticaria is a diseased condition that affects 0.5-1% of any given population at any given point of time. Immuno modulatory agents like cyclosporine, methotrexate and intravenous immunoglobulin can be used in refractory cases of chronic utricaria. The aim of present study is to assess the effectiveness, tolerability and safety of methotrexate in cases of chronic utricaria.

Material and methods: The present randomised controlled trial was conducted in the Department of Dermatology, venereology and leprology Moti lal Nehru Medical College Allahabad (U.P.) during a period of 1 year. This study was conducted from June 2013 to May 2014. The study enrolled 80 subjects who were randomly divided into two groups. Group I patients received methotrexate and Group II patients received placebo. A complete history of patients was obtained and assessment of utricaria was done on the basis of wheals/day, mean score of pruritis, size and duration of wheals and days of utricaria per week. Complete blood, urine, stool examination of all the patients were performed before beginning of the study. Follow up was done at 4 and 8 weeks to determine the severity of itching. Mann whitney test was applied as a test of significance to compare the results between case and control. P value of less than 0.05 was considered significant.

Result: The mean age of subjects in Group I was 35.33 +/- 4.53 years and in Group II were 34.21 +/- 5.35 years. There were 17 males and 23 females in Group I. In Group II, there were 40% males and 60% females. 30% of the subjects in Group I were single and rest 70% were married. The mean wheal duration changed from 2.76 to 0.89 in Group I and 2.03 to 0.48 in Group II. There was no significant difference in both the groups. The mean wheal episodes changed from 2.11 to 0.70 in Group I and 1.83 to 0.43 in Group II. There was no significant difference in both the groups. The urticaria episodes reduced from 6.32 in group I to 1.94 and in Group II they reduced from 6.68 to 1.03

Conclusion: Various treatment modalities are available for treating recalcitrant cases of urticaria. In our study the use of methotrexate didn't provide any additional advantage compared to placebo. There was improvement seen both in placebo group and methotrexate group.

Keywords: Methotrexate, Immunomodulatory, Randomised, Urticaria

INTRODUCTION

Chronic urticaria is a diseased condition that affects 0.5-1% of any given population at any given point of time. The duration of this condition varies from 1-5 years but it can last longer in cases of more severe forms like those associated with angioedema and autoreactivity.[1] It is characterised by recurring episodes that generally occur two times a week or for 6 weeks or even more.[2] It is a distressing condition that one frequently encounters in clinical practice. Diagnosis of this condition is solely based on clinical examination and hence investigations based on detailed clinical history and examination are done.[3] The main choice of treatment for symptomatic relief is non sedating antihistaminics chielf H1 antihistaminics but it provides relief to symptoms only in less than 50% cases.1 For these patients increasing the dose to four folds provides relief but this is also not true in all cases. Thus even with antihistaminics every third or fourth patient will be symptomatic. These patients are grouped into antihistaminics non responders.[4]

For such patients with resistant form of utricaria, additional medications are added like short term corticosteroids in cases of acute flare ups or high doses of 1st or 2nd generation H1 antihistaminics or tricyclic antidepressants such as doxepin etc. Since in chronic utricaria cases there is production of auto antibodies against Ig E or its receptor, therefore the use of immune modulatory agents was also advised by some. They have seen to provide relief in 30% of cases.[5,6] Immuno modulatory agents like cyclosporine, methotrexate and intravenous immunoglobulin can be used in refractory cases of chronic utricaria.[7-9] Methotrexate has been found to effective in idiopathic, autoimmune and steroid dependent types of chronic utricaria.[10-12] The aim of present study was to assess the effectiveness, tolerability and safety of methotrexate in cases of chronic utricaria.

MATERIAL AND METHODS

The present randomised controlled trial was conducted in the Department of Dermatology, Institute, state during a period of 1 year. This study was conducted from June 20XX to July 20XX. The study enrolled 80 subjects who were randomly divided into two groups. Group I patients received methotrexate and Group II patients received placebo. The study was approved by the Institution's ethical board and all the subjects were informed about the study and a written consent was obtained from all in their vernacular language.

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variable		Group I	Group II	P value
Age (Mean +/- SD)		35.33 +/-4.53	34.21 +/- 5.35	>0.05
Gender	Male	17(42.5%)	16(40%)	>0.05
	Female	23(57.5%)	24 (60%)	>0.05
Marital status	Single	12(30%)	11(27.5%)	>0.05
	Married	28(70%)	29(72.5%)	>0.05
occupation	Student	8(20%)	10(25%)	>0.05
	Housewife	17(42.5%)	18(45%)	>0.05
	Job	15(37.5%)	12(30%)	>0.05
Aggravating factors	None	25	28	>0.05
	Drug	11	13	>0.05
	Food	7	4	>0.05
	Sunlight	3	1	>0.05
Mean duration of disease (years)		1.8	2.1	>0.05
Family history of atopy		4	1	>0.05

Table-1: Socio demographic details of the study

Variable	0 Weeks	8 Weeks	P Value
Wheal score			
Group I (MTX)	2.39 (0.22)	0.65 (0.21)	>0.05
Group II (placebo)	2.48 (0.17)	0.43(0.22)	
Pruritis score			
Group I (MTX)	2.76 (0.15)	0.68 (0.22)	>0.05
Group II (placebo)	2.67 (0.36)	0.48 (0.20)	
Wheal size			
Group I (MTX)	2.18 (0.33)	0.66 (0.24)	>0.05
Group II (placebo)	1.37 (0.23)	0.58 (0.39)	
Wheal duration			
Group I (MTX)	2.76 (0.14)	0.89 (0.25)	>0.05
Group II (placebo)	2.03 (0.24)	0.48 (0.20)	
Wheal episodes			
Group I (MTX)	2.11 (0.25)	0.70 (0.28)	>0.05
Group II (placebo)	1.83 (0.13)	0.43 (0.26)	
Urticaria episodes			>0.05
Group I (MTX)	6.32 (0.22)	1.94 (0.85)	
Group II (placebo)	6.68 (0.30)	1.03 (0.42)	

Table-2: Comparison of baseline and results at the end of 8 weeks

Patients who were enrolled in this study had to stop their medications for one week so that baseline utricaria score could be established. Patients with utricaria less than 6 weeks old were excluded from the study and urticaria solely due to drugs, physical agents, foods etc were also excluded from the study. Pregnant or lactating mothers, patients on immunosuppressive drugs or any compromised medical condition were also excluded from the study. Group I patients were administered capsules that contained powdered methotrexate 15 mg per week for 3 months and Group II were given similar placebo.

A complete history of patients was obtained and assessment of utricaria was done on the basis of wheals/day, mean score of pruritis, size and duration of wheals and days of utricaria per week. Complete blood, urine, stool examination of all the patients were performed before beginning of the study. Follow up was done at 4 and 8 weeks to determine the severity of itching. All the blood tests were repeated to determine any abnormality in blood. If there was absence of wheals and pruritis without antihistaminics then it was defined as complete remission and reduction in wheals and pruritis from baseline but persistence of certain symptoms that require antihistaminics was defined as partial remission.

STATISTICAL ANALYSIS

All the data was arranged in a tabulated form and analysed using SPSS software. Mann whitney test was applied as a test of significance to compare the results between case and control. P value of less than 0.05 was considered significant.

RESULTS

The present study enrolled a total of 80 subjects, out of these 40 received methotrxate and 40 received placebo.

Table 1 shows the demographic details of the subjects. The mean age of subjects in Group I was 35.33 +/- 4.53 years and in Group II were 34.21 +/- 5.35 years. There were 17 males and 23 females in Group I. In Group II, there were 40% males and 60% females. 30% of the subjects in Group I were single and rest 70% were married. In Group II there were 72.5% married and 27.5% single subjects. 20% subjects in Group I were students, 42.5% were housewives and 37.5% had a job. In Group II, 25% were students, 45% were housewives and 30% had a job. In Group 1, 25patients had no aggravating factors and in Group II, 28 subjects had no aggravating factors. Drugs were the aggravating factor in 11 patients of Group I and 13 patients of Group II. Sunlight was the aggravating factor in 3 patients of Group I and 1 patient of Group II. The mean duration of disease was 1.8 years in Group I and 2.1 years in Group II. Family history of atopy was seen in 4 patients of Group I and 1 patient of Group II. There was no significant relation of demographics with utricaria as the p value was >0.05.

Table 2 shows the comparison of baseline and end results in both the groups. The mean wheal score changed from 2.39 to 0.65 in Group I and 2.48 to 0.48 in Group II. There was no significant difference in both the groups. The mean pruritis score changed from 2.18 to 0.66 in Group I and 1.37 to 0.58 in Group II. There was no significant difference in both the groups. The mean wheal size changed from 2.18 to 0.66 in Group I and 1.37 to 0.58 in Group II. There was no

significant difference in both the groups. The mean wheal duration changed from 2.76 to 0.89 in Group I and 2.03 to 0.48 in Group II. There was no significant difference in both the groups. The mean wheal episodes changed from 2.11 to 0.70 in Group I and 1.83 to 0.43 in Group II. There was no significant difference in both the groups. The urticaria episodes reduced from 6.32 in group I to 1.94 and in Group II they reduced from 6.68 to 1.03.

DISCUSSION

Managing cases of chronic urticaria are often time consuming and frustrating and it has both direct and indirect healthcare finances along with socio-economic implications as there is reduced performance by 20-30% in most cases.[13,14] Various drugs have been tried for managing cases of chronic resistant utricarias. Corticosteroids were initially used for management of such cases but in according to a retrospective study by Asero R et al there was remission in 50% cases by the use of 0.3-0.5 mg/kg of predinisolone. Initially a dose of 25 mg/day was given for three days which was followed by rapid tapering of the dose within 10 days. The cases of remissions were only treated by the use of antihistaminics.[15] however the use of corticosteroids is associated with many long term complications that adversely affect the treatment. Complications like hypertension, GI bleeding, glucose intolerance and weight gain have seen to affect the treatment outcome. Thus their use became restricted to only short duration of management.[16] Evidences have been shown in literature regarding the use of dapsone for management of chronic spontaneous urticaria. Use of dapsone was first published by I Boehm et al in the year 1999.[17] Now days methotrexate is used for the management of chronic utricaria cases. Methotrexate is basically an anti metabolite used for management of chronic inflammatory diseases.[18,19] Methotrxate acts through various mechanisms but in managing cases of urticaria its immunomodulatory and anti-inflammatory actions come into use.[20-22]

In the present study, the mean age of subjects in Group I was 35.33 +/- 4.53 years and in Group II were 34.21 +/- 5.35 years. There were 17 males and 23 females in Group I. In Group II, there were 40% males and 60% females. 30% of the subjects in Group I were single and rest 70% were married. In Group II there were 72.5% married and 27.5% single subjects. In Group 1, 25patients had no aggravating factors and in Group II, 28 subjects had no aggravating factors. Drugs were the aggravating factor in 11 patients of Group I and 13 patients of Group II. Sunlight was the aggravating factor in 3 patients of Group I and 1 patient of Group II. The mean duration of disease was 1.8 years in Group I and 2.1 years in Group II. Family history of atopy was seen in 4 patients of Group I and 1 patient of Group II. According to a study by Weiner, corticosteroid resistant case was successfully treated using methotrexate.[23] As per a study by Gach et al, methotrexate provided successful treatment to 2 cases of steroid dependent urticaria. [10] In a study conducted by Perez et al to retrospectively analyse the effect of methotrexate in managing cases of chronic urticaria they found that two patients showed complete response, 7 patients showed considerable benefit.[11] In our study, the mean wheal score changed from 2.39 to 0.65 in Group I and 2.48 to 0.48 in Group II. There was no significant difference in both the groups. The mean pruritis score changed from 2.18 to 0.66 in Group I and 1.37 to 0.58 in Group II. There was no significant difference in both the groups. The mean wheal size changed from 2.18 to 0.66 in Group I and 1.37 to 0.58 in Group II. . The urticaria episodes reduced from 6.32 in group I to 1.94 and in Group II they reduced from 6.68 to 1.03. In a study conducted by Vinod K. Sharma et al, the primary outcome was seen in only 3.5 ± 1.9 (out of 10) patients amongst the methotrexate group and in 3.67 ± 1.03 patients amongst the placebo group ($P > 0.05$).[24] The results of the study were in accordance with our study. The limitations of our study were smaller sample size and short follow up period. Increasing the duration of follow up period would have given a better outlook of the drug.

CONCLUSION

Managing cases of urticaria has always been an challenging issue. Various treatment modalities are available for treating recalcitrant cases of urticaria. In our study the use of methotrexate didn't provide any additional advantage compared to placebo. There was improvement seen both in placebo group and methotrexate group.

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