

A Randomised Single-Blind Pilot Study of Antihistamines and Placebo Versus add on Methotrexate Therapy in case of Chronic urticaria

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I. Introduction

Urticaria is derived from the word “urtica” which means “to burn or hives”. Urticaria is a skin condition consisting of wheal and flare reaction in which intra-cutaneous edema is surrounded by an area of redness that is typically pruritic, secondary to dermal edema and vasodilatation(1). Angioedema is characterised by sudden, erythematous, swelling of the lower part of the dermis and subcutis which may be associated with pain(2).

Urticaria is said to be a mast-cell mediate disease. It stimulates release of histamine and other inflammatory mediators which results in appearance of wheal and intense pruritus(3). Chronic Urticaria is common distressing disease characterized by spontaneous occurrence of wheals lasting for less than 24hrs with or without angioedema occurring daily or almost daily for 6 week or more without being related to a triggering or inducible factor identified as yet(1,4).

Evidences indicate that the disease urticaria was first introduced in the 10th century BC(5,6,7) and was said to be named as essera. In the 1792, the disease was presumed to be named as urticaria(8). Chronic Urticaria is a common disorder accounting for about 0.1% of the total population(9). The prevalence is more in the females compared to the males(10). Patient experience restrictions in daily life activity and social life due to uncompromising symptoms. Adolescent age group is estimated to be at a higher risk of developing major depression than those without Urticaria in similar age group(11). Establishing the cause of Urticaria is difficult and almost impossible. The exact pathogenesis of Urticaria is said to be due to degranulation of mast cell with release of histamine and other mediators. Histamine release causes erythema and flaring, sensory nerve stimulation of non-myelinated afferent c fibers leads to pruritus and increased permeability or extravasation of plasma causes edema and recruitment of neutrophils and eosinophils. Chronic urticaria may show presence of mononuclear cells, eosinophils, neutrophils, both eosinophils and neutrophils, basophils, mast cells and activated macrophages. Treatments of chronic Urticaria possess a therapeutic challenge for physicians and unsatisfactory outcome for the patients. The management option for this disease have undergone a sea of change over the last 2 or 3 decades and for that matter we hold a good position in treating the disease than in the past.(12,13)

II. Material And Methods

A single- blind randomised control trial was conducted on 70 patients of both gender ranging from age 18-50yrs with chronic urticaria attending the Out patient department of dermatology department of muzaffarnagar medical college, Muzaffarnagar, U.P. were included in the study. Patient were explained about the treatment, its side-effects and the outcome. A consent form was signed by each patient and all the patients were followed up for a week of 6weeks post treatment. Before starting the treatment planned, the patients were thoroughly evaluated for the confirmed diagnosis. The random division of patients was done in 2 groups. The duration of the treatment was 12weeks with a follow-up period of 6weeks. The subjective assessment was done on the basis of patient response as complete, partial and no response. The objective assessment was done using urticaria activity score. The baseline monitoring required for Methotrexate was done. Patients were asked about any adverse effects at each visit and unscheduled visits were allowed to report any side-effect if noted by the patients. The collective data was entered in excel and analysed using appropriate statistical methods with SPSS 16.0.2. The ‘p’ value was calculated and less than 0.05 was taken as significant. The grading of urticaria was done as urticaria free, well-controlled, mild, moderate, severe on the basis of the urticaria activity score¹² and the subjective assessment was done on the basis of remission rate.

Group A: All patients who qualified for the study after these investigations were given weekly oral methotrexate of 10 mg divided into 2 doses given 12 hourly, followed by 5 mg of folic acid except on the day of Methotrexate and 10mg levocetirizine once a day.

Group B: All the patients who were allotted this group were given 10mg of levocetirizine plus a placebo tablet.

III. Results

The present study was conducted in the department of dermatology, venereology and leprology at muzaffarnagar medical college, muzaffarnagar, uttar Pradesh. 70 patients suffering from chronic urticaria who fulfilled the inclusion and exclusion criteria and after taking proper consent were included in our study and were randomly divided into 2 groups. Group A of 35 patients was selected to give oral Methotrexate with antihistamine(levocetirizine),Group B of 35 patients was selected to give only oral Antihistamines(levocetirizine+placebo). Methotrexate was given in two divided doses of 5mg twice a day once weekly with folic acid 5mg except the day of Methotrexate with 10mg of levocetirizine. Group B were given 10mg of levocetirizine with placebo once daily. The females patients(41) outnumbered the male patients(29). Age of the patients ranged from 19-48yrs in both the groups. A complete history was taken and thorough examination of the patients was carried out in the study. The patients were then randomised into group A and group B. All the patients completed the treatment period for the duration of 12weeks with follow-up period of 6weeks for both the groups. The results were statistically analyzed using paired t test and the data was presented as MEAN±SD and —p value were calculated referring to appropriate tables. The value of —p (0.05 or less) was taken as statistically significant. The patients were graded on the basis of urticaria activity score and the improvement was graded on the basis of decrease in the urticaria activity score and subjective assessment was done using the remission response. The patients were called every week for follow-ups. On the basis of subjective and objective assessment patients were assessed weekly and Urticaria activity score was assigned and subjective assessment was done as complete response, partial response or no response. We compared the response at 0week, week 4, week 12 and follow up after 6 weeks. Patients were evaluated for any possible adverse effects (side-effects of Methotrexate+antihistamines) at each visit and unscheduled visits were allowed and recorded to report any such events. 23 patients in group 1 showed a complete response compared to group 2 in which only 13 patients showed a complete response at week 4 (table 1) (figure 1& 2). 7 patients in group 1 and 14 patients in group 2 showed a partial response. 5 patients in group1 showed no response while 8 patients in group 2 showed no response after the completion of the treatment (table2) (figure 3&4). 3 patients in group 1 and 8 patients in group 2 showed a relapse in follow-up period (table 3). 3 patients in group A showed few side-effects in response to the treatment which were hair thinning(1 patient) fatigue(1patient), mild headache(1patient). 2 patients in group B showed side-effect nausea (1patient), constipation (1patient). The mean ± SD of urticaria activity score for Methotrexate group at week 0 was 33.457 ± 6.946 whereas after completion of treatment at 12th week was 29.333 ± 10.994 which was statistically significant ($P<0.0379$)(table 4)(figure 5). The mean ± SD of urticaria activity score for antihistamine group at week 0 was 31.657 ± 7.996 whereas after completion of treatment at 12th week was 23.545 ± 12.06 which was statistically significant ($P<0.05$)(table 5)(figure 6). The comparative effect was statistically analysed p value came out to be $p<0.296$ (table 6) which was not significant, though the remission response was better in the Methotrexate group compared to the antihistamine group. Out of the total 70 patients 14.3%(5 patients) showed some minimal side-effects. 8.6%(3patients) in Methotrexate group and 5.7%(2 patients) in antihistamine group.

IV. Discussion

Chronic Urticaria is common distressing disease characterized by spontaneous occurrence of wheals lasting for less than 24hrs with or without angioedema occurring daily or almost daily for 6 week or more without being related to a triggering or inducible factor identified as yet^{1,4}. Chronic urticaria has found to be more common in adults compared to children with females being affected more than the males(14,15). The total female patients(41) outnumbered the total male patients on our study

Zuberbier T. et al Epidemiology of urticaria: a representative cross-sectional population survey A questionnaire survey was done 4093 patients. The patients were interviewed on phone and the life time prevalence and male to female patients were calculated out of the total patients, 70.3% of the patients were females. The life time prevalence of chronic urticaria was calculated to be 1.8%. QOL was markedly reduced for people with CU. Unlike other allergic diseases, there was no increased risk associated with higher education or social status. Prick tests found sensitization of ≥ 1 for type 1 allergens in 39.1% of patients. (16)

Clinicoepidemiologic features of chronic urticaria study was conducted by V.Surbhi et al in patients having positive versus negative autologous serum skin test: with an objective to study the clinicoepidemiologic features like age, sex, age of onset and duration, frequency and distribution of wheals, urticaria severity, angioedema and systemic manifestations in ASST-positive and ASST-negative patients A study of 100 Indian

patients. The age group ranged between 14 and 63 (mean, 32.69 ± 13) years. The total female patients were 69 compared to the total male patients who were 31 out of the total 100 patients.(17)

IK Altunay et al did a study on Clinical Observations on Acute and Chronic Urticaria: A Comparative Study. The study included 84 patients with urticaria; 57 (70,2 %) were females, 27 (29,8%) were male.s52 (61,9%) patients were grouped as Acute urticaria , 32 (38,1%) patients as Chronic urticaria after the end of the 6th week. 32 of 84 patients (%38,09) turned to chronic urticaria.(18)

Singh M et al did a study on the Evaluation of the causes of physical urticarias. A total of 500 patients with urticaria were evaluated. The detailed history and physical findings were recorded in a proforma and regularly updated during subsequent visits.The sex distribution was nearly equal and the ages ranged from 1 to 69 years. The mean age of onset of urticaria was 31.2 ± 13.5 years.(19)

Kulthanan K et al conducted a study Chronic idiopathic urticaria: prevalence and clinical course on the population of thailand. Aretrospectively review of the 450 case record forms of patients with Chronic Urticaria and/or angioedema was done. The median duration of Chronic idiopathic urticaria and autoimmune urticaria were 390 days and 450 days respectively. Out of a total number of 450 patients with Chronic Urticaria, 337(75%) were diagnosed as Chronic Idiopathic urticaria. 43(9.5%) had physical urticaria, while 17(3.8%) had infectious causes.(20)

The pathogenesis of chronic urticaria (CU) is said to be due to activation and subsequent degranulation of mast cells in the skin. The release of histamine and other pro-inflammatory mediators from degranulated mast cells leads to appearance of wheals and angioedema through increased capillary permeability and erythema, via vasodilation.(21)chronic spontaneous urticaria is still perceived as an uncontrollable and difficult to manage disease(22)There are several guidelines on the management of chronic urticaria. Several treatment modalities with varying success rates are currently in use. The therapeutic effects vary greatly. For effective treatment of chronic urticaria it is important to identify the cause and arrest the progression and provide symptomatic relief to the patient(23).The literature regarding the use of Methotrexate in chronic urticaria is not much. Our present study aimed to see the efficacy and safety of oral Methotrexate in chronic Urticaria.

Methotrexate (MTX) is a folate analogue used in many skin disorders.MTX binds dihydrofolate reductase (DHFR) and inhibits enzymes that require folate co-factors, which interferes with DNA synthesis in actively dividing cells, and the increase of AICAR enzyme system leads to enhanced release of adenosine into the blood. Adenosine increases IL6 secretion by human monocytes interleukin 8 (IL8) production by peripheral blood mononuclear cells, leucotriene B4 synthesis in neutrophils, and decreased synovial collagenase gene expression(24,25).

Perez A. et al study to assess the effectiveness of methotrexate in 16 patients with chronic urticaria treated with methotrexate was carried out. No response was noted to antihistamines and second-line agents. Twelve of 16 patients responded well to the treatment. Three showed some benefit, seven considerable benefits and two cleared. The dose of methotrexate given was 10–15 mg weekly. Methotrexate was well tolerated by all the patients and thus it was Concluded that Methotrexate may benefit chronic urticaria independently of the pathogenic mechanism, whether autoimmune or not(26).

Godse K. et al case study on the use of Methotrexate in autoimmune urticaria. Four (3 females and 1 male) who were recalcitrant to treatment with oral antihistamines were taken under the study. Methotrexate was tried in patients with autoimmune urticaria in a dose of 25 mg orally twice a day for 2 days per week. All 4 patients showed a remarkable effect in the form of reduction in whealing and itching in one month. It was concluded that methotrexate is a viable option for the treatment of resistant autoimmune urticaria(27).

Yadav S et al conducted a study to see the effectiveness, safety and tolerability of Methotrexate in Chronic Urticaria: At a Tertiary Care Centre. A total number of 80 patients were enrolled for the study of both chronic spontaneous urticaria and chronic inducible urticaria and were divided into 2 groups. Patients in group I were given capsules of powdered methotrexate 15 mg per week for 3 months and similar placebo were given to Group II. The mean wheal score changed from 2.39 to 0.65 in Group I and 2.48 to 0.48 in Group II. The mean wheal size change was noted from 2.18 to 0.66 in patients of Group I and 1.37 to 0.58 in Group II. The urticaria episodes reduced from 6.32 in group I to 1.94(28).

Montero Mora P. et aldesigned a case study Autoimmune Urticaria. Treatment with Methotrexate. Seven patients were enrolled in the study. Initially methotrexate was given at adose of 2.5 mg every 12 hours, two days a week the doses was increase to three days a week for a 6-week period after assessing any drug related toxicity in any of the patient. Improvement was observed in presence of spots, sleep disorders, itching and repercuSSION on daily activities. No adverse effects were noted in all the 7 patients(29).

The present study was to assess the efficacy and safety of oral Methotrexate in chronic Urticaria. The patients were graded on the basis of urticaria activity score and the improvement was graded on the basis of decrease in the urticaria activity score and subjective assessment was done using the remission response. The mean \pm SD of urticaria activity score for Methotrexate group at week 0 was 33.457 ± 6.946 which after completion of

treatment was 29.333 ± 10.994 which was statistically significant ($P < 0.0379$). The mean \pm SD of urticaria activity score for antihistamine group at week 0 was 31.657 ± 7.996 which after completion of treatment was 23.545 ± 12.06 which was statistically significant ($P < 0.05$). Thus the study hypothesised that Methotrexate is a safe, effective and useful, cost effective treatment option for the treatment of patients of chronic spontaneous urticaria not responding to antihistamines.

V. Conclusion

Methotrexate was found to be a safe, useful, cost effective, easily available drug for the treatment of chronic urticaria not responding to the baseline treatment. In our study we did not encounter any life threatening side-effects; however patients are still at risk of developing severe side-effects. Though the patients responded well to the treatment but the response rate was not 100%. Various treatment modalities have been tried in patients of chronic urticaria unresponsive to antihistamine and have shown some degree of efficacy but not much literature is available and all therapies have the potential of appearance of side-effect.

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TABLES

| Groups | Methotrexate + antihistamines group | Antihistamine group |
|---|-------------------------------------|---------------------|
| Complete remission | 16(45.7%) | 6(17.14%) |
| Partial remission | 12(34.3%) | 16(45.71%) |
| No response | 7(20%) | 14(40.00%) |
| Chi square value- 7.438 DF=2 P<0.02 (Significant) | | |

Table1:- Response rate noted at week 4.

| Groups | Methotrexate+antihistamine group | Antihistamine group |
|---|----------------------------------|---------------------|
| Complete remission (Symptom free) | 23(65.7%) | 13(37.14%) |
| Partial remission (<=50% improvement) | 7(20%) | 14(40.00%) |
| No response | 5(14.3%) | 8(22.85%) |
| Chi square value- 5.803 DF=2 P<0.05 (Significant) | | |

Table 2:- Response of patient after completion of treatment

| Groups | Methotrexate+antihistamine group | Antihistamine group |
|---|----------------------------------|---------------------|
| Complete remission | 15(42.85%) | 8(22.85%) |
| Partial remission | 12(34.28%) | 11(31.42%) |
| relapse | 8(22.85%) | 16(45.71%) |
| Chi square value= 4.841 DF=2 P<0.089(N/S) | | |

Table 3:- Response of patient after a follow-up period of 6 weeks

| | Group A | | | | P value |
|------|---------|----------------------|-----------------------|-----------|-----------------------|
| | 0 week | 4 th week | 12 th week | Follow up | |
| Mean | 33.457 | 26.63 | 29.333 | 27.05 | P<0.0379(significant) |
| S.D. | 6.946 | 11.557 | 10.994 | 10.694 | |

Table 4:- Effect of Methotrexate+ antihistamine at 0 week and its comparison with post treatment at week 4, week 8 and follow-up by using urticaria activity score

| | Group B | | | | P value |
|------|---------|----------------------|-----------------------|-----------|---------------------|
| | 0 week | 4 th week | 12 th week | Follow up | |
| Mean | 31.657 | 25.827 | 23.545 | 26.518 | P<0.05(significant) |
| S.D. | 7.996 | 11.374 | 12.06 | 12.481 | |

Table 5:- Effect of antihistamine+placebo at 0 week and its comparison with post treatment at week 4, week 8 and follow-up by using urticaria activity score

| | Group A | Group B |
|--------------|---------|---------|
| Mean | 29.33 | 23.545 |
| SD | 10.994 | 12.06 |
| P<0.296(N/S) | | |

Table 6:- Comparison of effect of treatment in group A(Methotrexate+antihistamine) and Group B(antihistamine+placebo) at week 12

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