

A Hospital Based Comparative Study to Evaluate the Efficacy of Methotrexate v/s Dapsone/ASST for Treatment of Chronic Urticaria

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Abstract

Background: Chronic Urticaria remains a major problem in terms of etiology, investigation, and management and causes comorbidity and high cost to the health care system. In our study, we are comparing the use of ASST, Dapsone and Methotrexate for the treatment of resistant chronic urticaria. So, these study findings will play an important role to determine treatment protocols for patients with chronic urticaria. **Materials & Methods:** A prospective comparative study done on 100 patients with chronic urticaria were selected from the patients attending out-patient clinic in Department of Dermatology, S.K. Government Medical College, Sikar, Rajasthan, India. The patients will be randomly allotted to any one of the following four treatment groups after calculating their Urticarial Activity Score (UAS) & Dermatology Life Quality Index (DLQI). Group A (Dapsone 50 mg), Group B (Methotrexate 10 mg), Group C (ASST) & control group. Patients were then divided into three categories based on these parameters into Good Responders, Average Responders & Poor Responders. **Results:** More than 76% of patients treated with ASST had good response to treatment while only 52% of those treated with dapsone and 32% of those treated with methotrexate had good response to treatment. Poor response was seen in 4% of ASST and Dapsone patients compared to the 20% in patients receiving Methotrexate. This is still better than the 60% with poor response in the control group. Side effects were more common in patients taking methotrexate with 3 out of 25 patients experiencing minor side effects while two patients taking dapsone also had documented side effects. **Conclusion:** Managing cases of urticaria has always been an challenging issue. Various treatment modalities are available for treating recalcitrant cases of urticaria. We concluded that ASST can be considered as a first line of treatment, Dapsone can be considered for patients refractory to treatment and Methotrexate is recommended as last resort, in patients who are refractory to other modalities of treatment.

Keywords: Chronic Urticaria, Dapsone, ASST, Methotrexate, DLQI.

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Introduction

Urticaria is defined as a skin lesion consisting of a wheal-and-flare reaction where the localized intracutaneous edema (wheal) is surrounded by an area of redness (erythema) that is typically pruritic. Individual lesions last as briefly as 30 minutes to as long as 36 hours. They can be as small as a millimeter or 6–8 inches in diameter (giant urticaria). They blanch with pressure as the dilated blood vessels are compressed, which accounts for the central pallor of the wheal[1,2].

Urticaria affects 15%–20% of the population. Lifetime prevalence of chronic urticaria varies from 0.05% to 23.6% in the general population, but a range of 1–5% seems more realistic. There is no racial variation in the incidence. Overall, urticaria is more common in women, with a female: male ratio of approximately 2:1 for chronic urticaria[3].

Chronic Urticaria remains a major problem in terms of etiology, investigation, and management and causes comorbidity and high cost to the health care system.

Chronic urticaria (CU) is a common skin disorder affecting 15–20% people in the general population. Based on its duration, frequency and causes, CU can be classified into three clinical subgroups, spontaneous (80%), physical (10%) and special forms (10%). Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is characterized by spontaneous occurrence of wheals without an obvious stimulus lasting for more than 6 weeks. Pathogenesis of CSU is unclear and possible causes may include chronic infections, allergy to certain food or food additives, anxiety, and autoantibody production against IgE receptor[4]. In our study, we are comparing the use of ASST, Dapsone and Methotrexate for the treatment of resistant chronic urticaria. So, these study findings will play an important role to determine treatment protocols for patients with chronic urticaria.

Materials & methods

A prospective comparative study done on 100 patients with chronic urticaria were selected from the patients attending out-patient clinic in Department of Dermatology, S.K. Government Medical College, Sikar, Rajasthan, India.

Inclusion Criteria

- Patients with Chronic Urticaria defined as urticarial eruption of more than 6 weeks duration characterized by hives or wheals.
- Age > 18 yrs
- Patient is resistant to treatment with anti histamines.

Exclusion Criteria

- Age below 18 yrs & above 60 yrs.

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- Physical urticaria / Urticaria secondary to an underlying medical condition.
- Pregnancy, lactating mothers and women wanting to conceive or underlying medical condition.
- Has taken any treatment other than anti histamines.

Study Procedure

Around 100 patients with chronic urticaria will be selected from the patients attending psoriasis out-patient clinic in Department of Dermatology. All patients will be explained about the disease, benefits & possible side effects of treatment.

Detailed history will be obtained, and patients will be evaluated as follows

- 1) General and systemic examination.
- 2) Dermatological examination.
- 3) Investigations namely complete hemogram, liver function tests, renal function tests autologous serum skin test and chest xray.
- 4) ENT & Dental opinion will be sought to rule out focal sepsis

The patients will be randomly allotted to any one of the following four treatment groups after calculating their Urticarial Activity Score (UAS) & Dermatology Life Quality Index (DLQI).

- Group A will comprise patients who will be given oral Dapsone 50 mg for a period of 12 weeks.
- Group B will comprise patients who will be given oral Methotrexate 10 mg (in 4 divided doses at 12 hourly interval) per week for a period of 12 weeks.
- Group C will comprise patients who will be given Treated with ASST (Autologous Serum Skin Therapy) – 2ml of autologous serum deep intramuscular injection once a week for 9 weeks.

In addition to these, patients in all the groups will be prescribed Antihistamines.

- Group D will be the control group who will receive only Antihistamines.

Follow-up

Patients will be reviewed every 4 weeks at 4, 8 & 12 weeks for complaints and assessing clinical improvement till completion of treatment and once every two months for six months following completion

Assessment of Parameters

Blood parameters will be repeated every four weeks or as and when required and Parameters like Urticarial Activity Score (UAS) and Dermatology Life Quality Index (DLQI) will be assessed at end of treatment and at end of six months following treatment. Patients were then divided into three categories based on these parameters into Good Responders, Average Responders & Poor Responders.

- Good Responders: Patients post treatment UAS score < 2 and DLQI score < 2
- Average Responders: Patients post treatment UAS score 2 - 4 & DLQI score 2 - 9
- Poor Responders: Patients post treatment UAS score > 4 and DLQI score > 10

The higher of the two scores is taken into consideration while classifying the groups.

Statistical Analysis

Calculated data were arranged in systemic manner, presented in various table and figures and statistical analysis was made to evaluate the objectives of this study with the help of Statistical Package for Social Science (SPSS) version 24.

Results

The present study observed that age of 100 patients ranged from 18-60 years. Most of the patients (56%) were in between 18-30 years. Females were the predominantly involved sex with male to female ratio of 0.43:1 (table 1).

Table 1: Age & Sex Distribution of Patients with Chronic Urticaria

Age / Sex	Male	Female	Total
18 - 30	17 (17%)	39 (39%)	56 (56%)
31 - 40	5 (5%)	22 (22%)	27 (27%)
41 - 50	3 (3%)	9(9%)	12(12%)
51- 60	5 (5%)	0 (0%)	5 (5%)
Total	30 (30%)	70 (70%)	100 (100%)

Regarding precipitating factors, food allergens were the most common precipitating factor accounting for 15% of the cases, followed by infections & inhalants like house dust seen in 10% of cases. The other precipitating factors were drugs and water related. 55% of the total patients had no specific aggravating or trigger factor for occurrence of symptoms (table 2).

Table 2: Prevalence of precipitating factors in chronic urticaria patient

Precipitating Factor	No. of Patients	Percentage
Food	15	15%
Infections	10	10%
Inhalant	10	10%
Drugs	7	7%
Aquagenic	3	3%
No Specific Factor	55	55%
Total	100	100%

More than 76% of patients treated with ASST had good response to treatment while only 52% of those treated with dapsone and 32% of those treated with methotrexate had good response to treatment. Poor response was seen in 4% of ASST and Dapsone patients compared to the 20% in patients receiving Methotrexate. This is still better than the 60% with poor response in the control group (table 3).

Table 3: Distribution of response to treatment of all four groups of patients

	Good	Average	Poor	Total
ASST	19 (76%)	5 (20%)	1 (4%)	25
Methotrexate	8 (32%)	12 (48%)	5 (20%)	25
Dapsone	13 (52%)	11 (44%)	1 (4%)	25
Control	2 (8%)	8 (32%)	15 (60%)	25
Total	42 (42%)	36 (36%)	22 (22%)	100 (100%)

The mean DLQI score across all the treatment groups when compared showed that, patients treated with ASST had the fastest and the maximal response. Both the initial response and the end point was better in ASST patients. Control group patients showed no significant improvement in DLQI score. The dapson and methotrexate treated patients had similar response profile but there was a difference in the number of patients responding (table 4).

Table 4: Average DLQI score of patients in different treatment groups

Months	ASST			Methotrexate			Dapsone			Control		
	Good	Ave.	Poor	Good	Ave.	Poor	Good	Ave.	Poor	Good	Ave.	Poor
0	8	15	18	7	11	16	7	10	15	5	9	14
3	5	7	13	4	7	12	2	7	10	3	7	11
6	1	4	7	1	5	10	1	4	8	2	5	10

There is a statistically significant difference in response to treatment to all three groups when compared to control, with it being highly significant in the ASST group. On comparing ASST with dapson or methotrexate, there is again a statistically significant difference in response while there was no statistically significant difference when comparing dapson and methotrexate.

Side effects were more common in patients taking methotrexate with 3 out of 25 patients experiencing minor side effects while two patients taking dapson also had documented side effects (table 5).

Table 5: Prevalence of side effects in each treatment group

Treatment group	No. of Patients	Total patients treated	Percentage
ASST	0	25	0%
Methotrexate	3	25	12%
Dapsone	2	25	8%
Control	0	25	0%
Total	6	100	20%

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[5,6].

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 prednisolone. 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[7], 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 been seen to affect the treatment outcome. Thus, their use became restricted to only short duration of management[8]. Evidences have been shown in literature regarding the use of dapson for management of chronic spontaneous urticaria. Use of dapson was first published by I Boehm et al in the year 1999[9]. Now days methotrexate is used for the management of chronic urticaria cases. Methotrexate is basically an anti metabolite used for management of chronic inflammatory diseases[10-11]. Methotrexate acts through various mechanisms but in managing cases of urticaria its immunomodulatory and anti-inflammatory actions come into use[12-14].

The present study observed that age of 100 patients ranged from 18-60 years. Most of the patients (56%) were in between 18-30 years. Females were the predominantly involved sex with male to female ratio of 0.43:1. Young females were the most commonly involved group. Twenty to thirty years was the susceptible age group along with female gender. This is in accordance with other Indian studies regarding the epidemiology of the disease.

One or other form of precipitating factor was present in more than half of all the patients involved in the study. The most commonly implicated precipitating factor in our study was food allergens followed by infections and inhalants. A study by Godse et al[15] showed that infections and food allergens were important precipitating factors in the Indian population.

In the ASST group, all patients had a significant reduction in their DLQI score with only one patient having poor response, which was explained by the fact that both those patients had a severe initial

presentation. The response was especially good among those in whom the autologous serum skin test was positive. This response to ASST was found to be in concurrence with studies by Bajaj et al[16] and Staubach et al[17]. Compliance was good and there was no evidence of relapse. The only factor which hinders with their use, especially in a government setup, is the technological expertise and the availability of centrifuge machines.

In the Dapsone group, again there was a statistically significant improvement in response compared to the control group, but they compared unfavourably with ASST treatment group. The initial response was slower than that of ASST but the end point was similar especially in those responding well to treatment. There was good compliance, even though a couple of patients had minor side effects. These findings had concordance with studies conducted by Cooke et al[18] and Engen et al[19].

In the methotrexate group, there was a comparatively slower reduction in the DLQI score with response starting only near the end of treatment. They were better off than the control group but both the initial response and the end points were poor when compared to ASST. They had a comparable response to the patients treated with dapson, but its use is limited in patients with anaemia and deranged LFT. With the anaemia commonly prevalent in our population this limits its use in patients. Moreover, the incidence of side effects was more in this group. Studies by Sharma et al[20] advised the use of methotrexate in those with chronic recalcitrant urticaria who don't respond to other treatment modalities.

Conclusion

Managing cases of urticaria has always been an challenging issue. Various treatment modalities are available for treating recalcitrant cases of urticaria. We concluded that ASST can be considered as a first line of treatment, in patients with chronic urticaria, especially in those who are positive for Autologous Serum Skin Test. Dapsone can be considered for patients refractory to treatment. Methotrexate is recommended as last resort, in patients who are refractory to other modalities of treatment. Side effects profile and its contraindication in patients with haematological problems, restrict its more common usage.

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