

ORIGINAL RESEARCH

To evaluate the efficacy of Methotrexate versus Dapsone/ASST in the treatment of chronic urticaria

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ABSTRACT

Aim: To evaluate the efficacy of Methotrexate versus Dapsone/ASST in the treatment of chronic urticaria.

Materials & methods: A prospective comparative study done on 200 patients with chronic urticaria were selected from the patients attending out-patient clinic in Department of Dermatology. The participants were assigned in a random manner to one of four treatment groups based on their Urticarial Activity Score (UAS) and Dermatology Life Quality Index (DLQI) calculations. Group A was comprise patients who were given oral Dapsone 50 mg for a period of 12 weeks. Group B was comprise patients who were given oral Methotrexate 10 mg (in 4 divided doses at 12 hourly interval) per week for a period of 12 weeks. Group C was comprise patients who were given Treated with ASST (Autologous Serum Skin Therapy) – 2ml of autologous serum deep intramuscular injection once a week for 9 weeks. Group D was the control group who were received only Antihistamines.

Results: More than 72% of patients treated with ASST had good response to treatment while only 56% of those treated with dapsone and 30% of those treated with methotrexate had good response to treatment. Poor response was seen in 6% of ASST and Dapsone patients compared to the 20% in patients receiving Methotrexate. This is still better than the 52% with poor response in the control group.

Conclusion: It has been determined that autologous serum skin test (ASST) may be regarded as an initial therapeutic approach for individuals diagnosed with chronic urticaria, particularly among those who exhibit positive results on the ASST. Dapsone may be regarded as a potential therapeutic option for patients who have shown resistance to conventional treatment methods. Methotrexate is typically advised as a final option for patients who have not responded to alternative treatment methods.

Keywords: Methotrexate, Dapsone, ASST, Chronic Urticaria

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Introduction

Urticaria, also known as hives, is characterised by the presence of a wheal-and-flare reaction on the skin. This reaction involves the formation of localised edoema, referred to as a wheal, which is accompanied by surrounding redness, known as erythema. It is worth noting that this condition is commonly associated with itching. The duration of individual lesions can range from a minimum of 30 minutes to a maximum of 36 hours. The size of these entities can range from as small as one millimetre to as large as six to eight inches in diameter, commonly

referred to as giant urticaria. The blanching observed in this context is a result of the application of pressure, causing the compression of dilated blood vessels. This compression is responsible for the central pallor observed in the wheal [1,2]. Urticaria has a prevalence rate of approximately 15%–20% among the general population. The lifetime prevalence of chronic urticaria exhibits a wide range of estimates, spanning from 0.05% to 23.6% in the general population. However, a more plausible range of 1-5% appears to be a more accurate representation. The incidence does not exhibit any racial variation. In

general, the prevalence of urticaria is higher among women, exhibiting a female-to-male ratio of approximately 2:1 in cases of chronic urticaria [3]. Chronic urticaria continues to pose significant challenges in terms of its aetiology, investigation, and management, leading to comorbidity and imposing substantial costs on the healthcare system. Chronic urticaria (CU) is a prevalent dermatological condition that impacts approximately 15-20% of individuals within the general population. CU can be categorised into three distinct clinical subgroups based on its duration, frequency, and underlying causes. These subgroups include spontaneous CU, which accounts for approximately 80% of cases, physical CU, which accounts for about 10% of cases, and special forms of CU, which also account for approximately 10% of cases. Chronic spontaneous urticaria (CSU), alternatively referred to as chronic idiopathic urticaria, is distinguished by the spontaneous manifestation of wheals without a discernible stimulus, persisting for a duration exceeding six weeks. The pathogenesis of chronic spontaneous urticaria (CSU) remains uncertain, with potential etiological factors including chronic infections, food allergies or sensitivities to specific food additives, anxiety, and the production of autoantibodies targeting the IgE receptor [4]. In the present study, we aim to conduct a comparative analysis of the utilisation of ASST, Dapsone, and Methotrexate as potential therapeutic interventions for managing cases of chronic urticaria that have proven to be unresponsive to conventional treatment methods. The study findings have played a significant role in establishing treatment protocols for patients diagnosed with chronic urticaria.

Materials & methods

A prospective comparative study done on 200 patients with chronic urticaria were selected from the patients attending out-patient clinic in Department of Dermatology.

Inclusion Criteria

- Patients with Chronic Urticaria defined as urticarial eruption of more than 6 weeks duration characterized by hives or wheals.
- Age > 20yrs
- Patient is resistant to treatment with anti histamines.

Exclusion Criteria

- Age below 18 yrs & above 60 yrs
- 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.

Methodology

Approximately 200 individuals diagnosed with chronic urticaria were chosen from the pool of patients seeking treatment at the psoriasis out-patient clinic within the Department of Dermatology. The disease, as well as the potential benefits and possible side effects of treatment, were thoroughly explained to all patients. A comprehensive medical history was collected, and patients underwent various evaluations including a general and systemic examination, dermatological examination, and a series of investigations such as complete hemogram, liver function tests, renal function tests, autologous serum skin test, chest x-ray, and consultation with ENT and Dental specialists to exclude the possibility of focal sepsis. The participants were assigned in a random manner to one of four treatment groups based on their Urticarial Activity Score (UAS) and Dermatology Life Quality Index (DLQI) calculations.

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

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

Patients were 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 were repeated every four weeks or as and when required and Parameters like Urticarial Activity Score (UAS) and Dermatology Life Quality Index (DLQI) was 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 23.

Results

The current study examined a sample of 200 patients, whose ages spanned from 20 to 60 years. The majority of the patients (55%) fell within the age range of 20-30 years. Women were the primary gender involved, with a male to female ratio of 0.41:1 (see Table 1).

Table1: Age & Sex Distribution of Patients with Chronic Urticaria

Gender	Number	Percentage
Male	58	29
Female	142	71
Age		
20 - 30	110	55
30 - 40	52	26
40 - 50	26	13
50- 60	12	6

Regarding precipitating factors, food allergens were the most common precipitating factor accounting for 14% of the cases, followed by infections & inhalants like house dust seen in 11% of cases. The other precipitating factors were drugs and water related. 59% 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	28	14
Infections	22	11
Inhalant	22	11
Drugs	10	5
Aquagenic	4	2
No Specific Factor	118	59
Total	200	100

More than 72% of patients treated with ASST had good response to treatment while only 56% of those treated with dapsone and 30% of those treated with methotrexate had good response to treatment. Poor response was seen in 6% of ASST and Dapsone patients compared to the 20% in patients receiving Methotrexate. This is still better than the 52% 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	36 (72%)	11 (22%)	3 (6%)	50
Methotrexate	15 (30%)	25(50%)	10 (20%)	50
Dapsone	28 (56%)	21 (42%)	1 (2%)	50
Control	13 (26%)	11 (22%)	26 (52%)	50
Total	92 (46%)	68 (34%)	40 (20%)	200 (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 dapsone 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	9	16	19	8	12	17	8	11	16	6	10	15
3	6	8	14	5	8	13	3	8	11	4	8	12
6	2	5	8	2	6	11	2	5	9	3	6	11

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 dapsone or methotrexate, there is again a statistically significant difference in response while there was no statistically significant difference when comparing dapsone and methotrexate.

Side effects were more common in patients taking methotrexate with 5 out of 50 patients experiencing minor side effects while two patients taking dapsone 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	50	0%
Methotrexate	5	50	10%
Dapsone	3	50	6%
Control	0	50	0%
Total	8	200	16%

Discussion

The management of chronic urticaria can be a laborious and vexing task, resulting in significant healthcare expenditures and socio-economic consequences. Moreover, it is frequently associated with a decline in performance, typically ranging from 20% to 30% [5,6]. Corticosteroids were initially employed for the treatment of these cases; however, a retrospective study conducted by Asero R et al revealed that a remission rate of 50% was achieved through the administration of prednisolone at a dosage range of 0.3-0.5 mg/kg. The administration of a 25 mg/day dosage was initiated for a duration of three days, after which the dosage was promptly reduced over a period of 10 days. The instances of remissions were exclusively managed through the administration of antihistaminics [7]. Nevertheless, the utilisation of corticosteroids is linked to numerous enduring complications that detrimentally impact the efficacy of the treatment. Complications such as hypertension, gastrointestinal bleeding, glucose intolerance, and weight gain have been observed to impact the outcome of treatment. Consequently, their utilisation was limited exclusively to brief periods of administration [8]. Literature has presented evidence regarding the utilisation of dapsone for the treatment of chronic spontaneous urticaria. The initial publication on the utilisation of dapsone was authored by Boehm et al. in 1999 [9]. Currently, methotrexate is employed for the treatment of chronic urticaria cases. Methotrexate is an anti-metabolite commonly employed in the treatment and control of chronic inflammatory conditions [10-11]. Methotrexate exerts its therapeutic effects through multiple mechanisms, particularly in the treatment of urticaria, where its immunomodulatory and anti-inflammatory properties are employed [12-14]. The current study examined a sample of 200 patients, whose ages spanned from 20 to 60 years. The majority of the patients (55%) fell within the age range of 20-30 years. Females exhibited a higher level of involvement, with a male to female ratio of 0.41:1. The demographic group that exhibited the highest level of involvement was young females. The age group most susceptible to the condition was between twenty and thirty years, with a higher prevalence observed among individuals identifying as female. This finding aligns with previous research conducted in India pertaining to the epidemiology of the disease. A precipitating factor, in one form or another, was observed in over 50% of the patients included in the study. The precipitating factor most

frequently implicated in our study was food allergens, with infections and inhalants following closely behind. In a study conducted by Godse et al. (15), it was demonstrated that infections and food allergens played significant roles as precipitating factors within the Indian population. Within the ASST group, it was observed that all patients experienced a notable decrease in their Dermatology Life Quality Index (DLQI) score, except for a single patient who exhibited a suboptimal response. This outcome can be attributed to the severe initial manifestation of the condition in both of these individuals. The reaction was particularly favourable among individuals who tested positive for the autologous serum skin test. The response to ASST was determined to be consistent with the findings of Bajaj et al (16) and Staubach et al (17), as supported by previous studies. The level of compliance exhibited by the participants was deemed satisfactory, and no indications of relapse were observed. The primary obstacle to their utilisation, particularly within a governmental context, pertains to the level of technological proficiency and the accessibility of centrifuge apparatus. Within the cohort receiving Dapsone, a statistically significant enhancement in response was observed when compared to the control group. However, the outcomes of the Dapsone group were less favourable in comparison to the ASST treatment group. The initial reaction exhibited a slower rate compared to ASST; however, the final outcome was comparable, particularly among individuals who responded favourably to the treatment. Despite a few patients experiencing minor side effects, overall compliance was satisfactory. The results of this study were consistent with previous research conducted by Cooke et al [18] and Engen et al [19]. Specifically, in the group receiving methotrexate, there was a relatively slower decrease in the DLQI score, and a response was observed towards the end of the treatment period. The experimental group exhibited a higher level of improvement compared to the control group. However, it is important to note that both the initial response and final outcomes were suboptimal in comparison to the ASST. The patients treated with dapsone exhibited a response that was similar in nature. However, the administration of dapsone is restricted in patients who have anaemia and abnormal liver function tests. The high prevalence of anaemia within our population restricts its applicability in patient cases. Furthermore, the prevalence of adverse effects was higher within this cohort.

Conclusion

The management of urticaria has consistently posed a significant challenge. There exist multiple treatment modalities that can be utilised in the management of refractory cases of urticaria. It has been determined that autologous serum skin test (ASST) may be regarded as an initial therapeutic approach for individuals diagnosed with chronic urticaria, particularly among those who exhibit positive results on the ASST. Dapsone may be regarded as a potential therapeutic option for patients who have shown resistance to conventional treatment methods. Methotrexate is typically advised as a final option for patients who have not responded to alternative treatment methods. The side effects profile and contraindications in patients with haematological disorders limit the widespread use of this treatment.

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