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Histaglobulin: An Elixir for Treatment of Chronic Urticaria

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Abstract

Chronic Urticaria (CU) is a persistent, distressing skin condition characterized by the daily or almost daily occurrence of itchy, spontaneous wheals for more than six weeks. Traditional treatments often involve nonsedative antihistamines and immunomodulators, which may not provide long-term relief. Histaglobulin, combining histamine dihydrochloride and human immunoglobulin, has been evaluated for its potential to improve treatment outcomes in CU. Aim of the study was to assess the efficacy of histaglobulin in reducing the severity of symptoms in patients with chronic spontaneous urticaria and its ability to decrease the dependency on antihistamines. A single-centre, open-label, prospective clinical study was conducted at Mamata General Hospital's Dermatology Venereology and Leprosy Outpatient Department from October 2023 to May 2024. Thirty patients aged 18-60 with chronic spontaneous urticaria were enrolled after obtaining informed consent. Patients were administered a subcutaneous injection of histaglobulin weekly for eight weeks and followed up until the 24th week. The primary outcome measure was the change in the Urticaria Activity Score over 7 days (UAS 7) from baseline to week 8. Out of 30 patients, 28 completed the study. The initial mean UAS 7 score was 28, which reduced to 10 by week 8, indicating a 64% reduction. Eight patients (35%) achieved complete response (UAS 7 = 0). All participants who completed the study reduced or stopped their antihistamine usage. The improvement was statistically significant ($p<0.0001$). Histaglobulin significantly reduced the severity of urticaria symptoms and the use of rescue medication in patients with chronic spontaneous urticaria. It was well-tolerated with no adverse effects reported, suggesting its utility as an effective alternative to traditional therapies, potentially offering long-term remission.

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Key Words

Chronic spontaneous urticaria, histaglobulin, treatment, UAS 7, antihistamines, immunotherapy

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INTRODUCTION

Urticaria is a heterogeneous skin disorder, characterized by raised, well-defined areas of erythema, swelling and itching, which are commonly known as "hives". These lesions appear on different parts of the body and they resolve spontaneously without any scar or residual pigmentation. In the general population, up to 20% of people develop urticaria sometime in their lifetime. Although in majority of the patients it is self-limiting in nature, chronic nature is observed in few patients. The prevalence of chronic urticaria is about 0.5-1% of the total population[1].

Chronic Urticaria (CU) is a distressing dermatosis of skin and is defined as urticaria persisting daily or almost daily for more than six weeks and where a predominant physical cause has been excluded. CU can be associated with the various auto-immune conditions including thyroid disorder, vitiligo, rheumatoid arthritis and pernicious anaemia. It also causes significant effect on the quality of life of the patient[2].

Various therapeutic options are available for the treatment of CU. First in the treatment ladder are nonsedative antihistamines, which are initially started at low doses followed by escalation of the dosage of these agents and the addition of a leukotriene antagonist. The use of immunomodulators, such as cyclosporin, methotrexate, omalizumab and dapsone, is a last resort for treating this condition[3]. CU has an unpredictable, relentless course and often shows a poor response to drug treatment. It can be challenging to determine the appropriate medication to suit the patient. The need for long term and daily intake of these agents is frustrating and may lead to non-compliance. Treatment options which increase the duration of remission and those which address the key factors involved in the disease pathogenesis are the need of the hour[4]. Thus, the present study was done to assess the effectiveness of injection histaglobulin, a complex of histamine and human immunoglobulin, in producing relief in patients with CU.

MATERIALS AND METHODS

A single centre, open label, prospective clinical study was carried out with 30 patients of chronic spontaneous urticaria presenting to outpatient department in the Dermatology Venereology and Leprosy (DVL) Out Patient Department (OPD) in Mamata General Hospital from October 2023 to May 2024 after obtaining the approval from the Institutional Ethics Committee.

Inclusion Criteria: Patients diagnosed with chronic spontaneous urticaria of age 18-60 years and either gender presenting to OPD were included in study after obtaining informed consent. Chronic spontaneous urticaria was diagnosed if the patient had a history of daily or almost daily occurrence of widespread, itchy, spontaneous wheals for a period of more than six weeks, with individual lesion lasting less than 24 hours and patients negative for ASST were included.

Exclusion Criteria: Patients younger than 18 years, pregnant and lactating mothers, patients on long term immunosuppressants for CU and those with any other co-morbidities were excluded from the study. Physical urticaria such as cold induced, pressure, heat contact, solar, dermographic, vibratory, aquagenic, cholinergic and drug induced urticaria were also excluded from the study.

Baseline Evaluation: After obtaining informed consent, clinical examination of the patient was done and a detailed history regarding the duration, severity, diurnal variation of lesions, any associated systemic co-morbidities, such as thyroid disorders, diabetes mellitus, or hypertension, any concomitant drug use by the patient and a history suggestive of any physical form of urticaria or urticarial vasculitis was taken. This was followed by routine investigations like complete blood count with differential count, absolute eosinophil count, complete urine examination, stool examination for ova and cysts, thyroid profile, renal and liver function tests. The baseline UAS 7 score was calculated and the number and type of oral antihistamine the patient was taking in the past week were recorded. The UAS 7 was calculated based on European Academy of Allergy and Clinical Immunology (EAACI) guideline 2013. UAS 7 a unified, validated and simple scoring system is a sum of daily pruritus score (0-none, 1-mild, 2-moderate, 3-severe) and daily wheal score (0-none, 1-one to six wheals, 2-seven to twelve wheals, 3-more than 12 wheals). The sum of the score (0-6) for each day is summarized over one week, with a maximum of 42. Higher scores indicate more severe disease. ASST was then performed as per the standard procedure and patients who were negative for this test are taken into the study.

Treatment Schedule and Follow Up: The patients were administered a subcutaneous injection of 1mL Histaglobulin (HISTOGLOB® manufactured by Bharat Serums and Vaccines Ltd., Maharashtra, India), which is a combination of human normal immunoglobulin (12 mg) and histamine dihydrochloride (0.15 mcg) over the arm, weekly for eight consecutive weeks. Patients were also prescribed rescue medication (tablet levocetirizine 5 mg) to be taken when required, not exceeding the permitted daily dosage. During each weekly visit, the response to treatment was assessed using UAS 7. The number of rescue medications taken in the past week was also noted. A final assessment was done at 24th week of starting the therapy.

Statistical Analysis: Statistical analysis was carried out using SPSS software (version 25.0). A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSIONS

The (Table 1) presents demographic information from a clinical study involving 30 patients diagnosed with chronic spontaneous urticaria. Of these, 28 patients completed the treatment protocol, while 2 patients dropped out due to a poor response to treatment. The gender distribution of the participants included 14 males and 16 females, indicating a slightly higher participation rate among females, which is consistent with the higher prevalence of the condition in females. The mean age of the participants was 39 years and the average duration of the disease prior to the study was 24 months. This information helps contextualize the study population in terms of age, gender, disease duration and adherence to the treatment regimen.

The (Table 2) summarizes the response to treatment at week 8 for patients participating in a clinical study of chronic spontaneous urticaria. The initial Urticaria Activity Score over 7 days (UAS 7) for patients at the start of the study was 28, indicating a moderate level of disease severity. By week 8, the average UAS 7 score decreased to 10, reflecting a 64% reduction in symptom severity, which demonstrates a significant improvement due to the treatment. Furthermore, 35% of the patients, totaling 8 out of the 28 who completed the study, achieved a complete response, with their UAS 7 score reducing to zero, indicating no symptoms of urticaria at the end of the treatment period. The highly significant p-value of less than 0.0001 confirms that the observed reduction in symptoms is not due to random chance but is statistically significant. This strong statistical support underscores the effectiveness of the treatment in substantially alleviating the symptoms of urticaria among the study participants.

The (Table 3) shows the outcome related to antihistamine medication usage for the 28 patients who completed the clinical study on chronic spontaneous urticaria. It indicates that all of these patients, which represent 100% of those who completed the study, were able to either reduce or completely stop their use of antihistamine medications by the end of the treatment protocol. This suggests a significant therapeutic benefit from the treatment regimen employed in the study, demonstrating not only a reduction in symptoms (as reflected in the UAS 7 scores) but also a decrease in the need for regular antihistamine medication, which is commonly used to manage symptoms in urticaria patients.

Chronic Urticaria (CU) is heterogeneous in its course, clinical picture and underlying causes. Common causes of CU include autoreactivity, physical urticaria and infection. Treatment of CU should be aimed at curing the condition whenever possible. This requires the identification of the underlying cause and measures taken against it[4]. CU became a perennial health problem that affects the quality of life of patients. Nonsedating antihistamines remain the main stay of treatment of CU[5-8]. Although it provides immediate relief from symptoms, it does not alter the immunopathogenesis or the natural course of the disease. There remains a challenge to find a drug which provides long-term benefit by acting on early steps in the immunological cascade, thereby preventing the attacks of urticaria.

Various immunological agents that are being used are oral corticosteroids, cyclosporine, methotrexate, intravenous immunoglobulin, omalizumab, tacrolimus, etc., Studies supporting the use of these drugs are limited and the side effect profile of all these drugs is also not favorable[7]. Immunotherapies such as allergen-specific immunotherapy, autologous serum therapy and autologous whole blood therapy have also been used with moderate success. Generation of anti-idio-type antibodies to various mast cell degranulating agents has been proposed as the mechanism of action of immunotherapy[9-11].

In this context, histaglobulin, a sterile preparation of histamine dihydrochloride coupled to active protein fraction extracted from human blood (gamma globulin) in strictly defined proportions, is a useful alternative. Gamma globulin used in HISTOGLOB® is tested negative for hepatitis b surface antigen, HIV-1, 2 antibodies and hepatitis C virus-ribonucleic acid by polymerase chain reaction as declared by the manufacturer[12].

Histaglobulin when injected into the body stimulates the production of antihistaminic antibody which fixes and neutralises the released histamine to the allergic reaction. Repeated doses of histaglobulin increase the antibody titer, for which it is recommended to administer doses every six months to maintain optimal titre of antibody. Serum histamine binding capacity in a normal individual is 20-30% and in allergic patients, it is only 0-5%. Histaglobulin treatment decreases IgE levels and it is hypothesised that the serum binding capacity of a patient to histamine increases[13]. Histaglobulin has been widely used in the treatment of allergic rhinitis. It is also used in various allergic disorders such as asthma, atopic dermatitis, CU, erythema multiforme and cutaneous drug allergy[14,15].

In present study, female patients outnumbered male patients (14 vs 16) as known that CU is more common in females[16]. The reason for that can be a small sample size of this study or tertiary care more accessible to males as compared to females. Mean duration of urticaria was 24 months. There was a significant reduction in UAS 7 from baseline to week 8

Table 1: Demographic information of study population

Description	Value
Total Patients	30
Patients Completed	28
Dropouts	2
Male Patients	14
Female Patients	16
Mean Age (years)	39
Mean Duration (months)	24

Table 2: Treatment response at week 8

Outcome Measure	Value
Initial UAS 7 Score	28
Final UAS 7 Score at Week 8	10
Percentage Reduction in UAS 7	64%
Patients with Complete Response (UAS 7 = 0)	8 (35%)
P-Value	<0.0001

Table 3: Medication usage

Description	Value
Antihistamine Use Reduction/Stopped	All patients who completed (100% of 28)

which indicates therapeutic benefit of histaglobulin maintained even after discontinuing it. Possible mechanism for this effect can be persistent level of antihistamine antibody titre even after stopping histaglobulin therapy. All the 28 patients who completed the study showed improvement in UAS 7. Total of 35% patients (8 patients) showed complete response at week 8 (UAS 7 = Zero). In all the patients who completed the study, antihistamine use could be reduced or stopped which proves the therapeutic benefit of histaglobulin. Thus, histaglobulin can be a useful addition in dermatologist armament against urticaria.

CONCLUSIONS

Histaglobulin is an important adjuvant in management of Chronic Urticaria. Patients of CU perceived a significant improvement in symptoms during the treatment period and it produced long-term remission too along with reducing the antihistamine requirement in majority of patients. It is safe, well-tolerated and no adverse effects have been observed, making it an effective management option than the existing treatment modalities.

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