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**Original Research Article**

# Autologous serum therapy in chronic spontaneous urticaria: useful in both ASST positive and negative patients

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## ABSTRACT

**Background:** Chronic urticaria is a common disorder that affects 0.1% of the population. Point prevalence is between 0.5 and 1.0% for chronic spontaneous urticaria. Functional IgG antibodies against IgE or high-affinity IgE receptors can be detected in 25-30% of patients with chronic spontaneous urticaria. Autologous serum therapy is a novel and cost-effective therapy. The aim of the study was to evaluate Autologous serum therapy's (AST) efficacy in chronic urticaria patients.
**Methods:** 106 patients with chronic urticaria were enrolled. Patients were categorized into two groups based on autologous serum skin therapy- ASST positive and ASST negative. Intramuscular injection of 0.05 ml/kg of autologous serum was injected every week for up to 9 weeks. Urticaria activity scoring (UAS) questionnaire was used to quantify the symptoms before the therapy and at nine weeks.
**Results:** Significant improvement in urticaria activity score was noted in both groups of the patients from the baseline and at nine weeks. (UAS reduced from 15.3 to 10.8 in ASST positive patients, and in ASST negative patients, UAS decreased from 16.2 to 10.1).
**Conclusions:** Both ASST positive and ASST negative patients showed significant improvement at nine weeks after starting autologous serum therapy. AST can be an effective modality for both patients.

**Keywords:** Chronic urticaria, Autologous serum skin test, Autologous serum therapy, Urticaria activity score, Autoimmune urticaria, High affinity IgE receptors

## INTRODUCTION

Urticaria is a vascular reaction of the skin characterized by wheals, angioedema or both and has been recognized since the days of Hippocrates.[1] Urticaria can be spontaneous or inducible. Based on the duration of disease activity, urticaria may be acute or chronic. In acute urticaria, the disease resolves in less than six weeks and in chronic, the condition continuously lasts for six weeks or more.[2]

Urticaria is a disabling condition and can prevent the patient from performing daily activities and has significant detrimental effects on the quality of life, with sleep deprivation and psychiatric comorbidity.

Chronic urticaria is a common disorder that affects 0.1% of the population.[3] The peak incidence of chronic spontaneous urticaria is in the fourth to fifth decades of life.[3] The cause of chronic urticaria varies. In general, infection, food, food additives, drugs, stress and thyroid disorders are the common causes.[2] No cause can be identified in about 30-50% of chronic urticaria cases and are labelled as chronic idiopathic urticaria.[4] Functional Immunoglobulin G (IgG) antibodies against Immunoglobulin E (IgE) or high-affinity IgE receptors can

be detected in 25-30% of patients with chronic spontaneous urticaria.[5] These antibodies degranulate mast cells and result in urticaria.

These patients show increased severity and duration of attacks of urticaria. Though the mainstay of treatment of chronic urticaria is by administering antihistamines, the subtype of chronic urticaria with IgG antibodies against IgE or high-affinity IgE receptors may require immunosuppressives or immunomodulators.

The gold standard for testing these antibodies is by basophil histamine release assay.[6] Autologous serum skin test (ASST) is a simple and inexpensive screening method that detects the histamine-releasing antibodies, first introduced by Grattan et al. and later standardized by Sabroe et al.[7,8] By doing ASST, we can identify the subset of chronic urticaria patients with histamine-releasing antibodies and can change the management strategy of those patients.

In Autologous serum therapy (AST), patients serum-containing tolerance generating antibodies to mast cell degranulating antigen are injected intramuscularly every week for nine weeks. AST is found to be effective in chronic urticaria patients.[9,10] In our study AST was reasonably effective in both ASST positive and ASST negative patients.

## METHODS

The study was designed as a single centre-based study, Institutional ethical permission was obtained prior start of the study. Written inform consent was obtained from the patients confidentiality was maintained. The duration of the study was from January 2020 to march December 2020. Sample size was calculated using the flowing formula:

$$N = Z^2 \frac{(1-\propto)}{2} \times \frac{pq}{d^2}$$

Z standard of 1.96, p (prevalence of ASST positivity): 34%, q (100-p): 66, d (absolute precision): 15.[12] All the diagnosed chronic urticaria patients attending the dermatology OPD and consenting for the study were included. The operational definition of chronic urticarias is the development of wheals occurring almost daily for more than six weeks. Exclusion criteria were pregnant, age below 18 years, Immunosuppressed patients, patients not able to come for weekly follow up, physical urticaria, uncontrolled diabetes mellites and patients on anticoagulants.

During the first visit, a thorough clinical examination was done. All patients were subjected to routine blood investigations, routine urine examination, Liver function tests (LFT), Renal function test (RFT), serological tests for syphilis like Venereal Disease Research Laboratory test (VDRL) and Treponema pallidum haemagglutination assay (TPHA), thyroid function test, Hepatitis B surface antigen (HBsAg), antibody to Hepatitis C virus (Anti-HCV) and an Anti-nuclear antibody test (ANA).

Urticaria activity is assessed according to the urticaria activity score 7 (UAS7) proposed by the European Association of Allergy and Clinical Immunology and the World Allergy Organization.[11] The activity is assessed under two headings- number of wheals and intensity of itching. The number of wheels: the disease is mild if there are only less than 20 wheals, moderate if the number is between 20 and 50 and intense if the number is more than 50 in 24 hours.

The intensity of itching: The itching is mild if the itching is not annoying or troublesome, moderate if the itching is troublesome but does not interfere with normal daily activity or sleep and severe if the itching is sufficiently troublesome to interfere with normal daily activity or sleep. The USA is assessed during the first week and consecutively every week while on autologous serum therapy for up to 9 weeks.

### *Autologous serum skin test*

Antihistamine and corticosteroids are withdrawn 48 hours before the procedure. After cleaning the site with antiseptic, 5 ml of venous blood is collected in a glass tube without additives. The blood is allowed to clot, and the sample is centrifuged at 2000 revolutions per minute for 15 min. The undiluted serum is collected in a sterile syringe. The site for ASST is the volar forearm skin. We avoid skin known to have had spontaneous wheals in the previous 48 hours. This avoids areas where mast cells are refractory to further activation (local tachyphylaxis). The test site is cleansed with an antiseptic, 0.05 ml of undiluted serum injected intra-dermally. As a negative control, 0.05 ml of normal saline was injected intra-dermally. Positive histamine control was not done in our study due to logistic issues. The test result was read after a waiting period of 30 min. A positive autologous serum skin testing was defined as wheal and flare of 1.5 mm or more than the saline induced response at 30 min.

For autologous serum therapy, 5 ml of venous blood was collected in a red vacutainer and centrifuged at 3000 rotations per minute for 15 min. Serum at a dose of 0.05 ml/kg body weight was injected intramuscularly. This procedure was repeated weekly for up to 9 weeks.

Data were entered in Microsoft excel and data was analysed using SPSS software. Continuous variables were expressed as mean and categorical variables like gender, occupation, history of atopy, number of wheals, intensity of itching, duration of wheals and laboratory investigations were expressed as proportions.

Chi square statistic was done for testing the significance.

## RESULTS

A total of 120 chronic urticaria patients were enrolled, but 14 patients dropped out of the study after one or more autologous serum injections. Thus, 106 patients completed the study and were included in the study's final analysis.

The mean age of the patients was 23.5±9 years. The majority of the patients were in the second and third decades of life. The majority of the patients were females (73 patients). Among them, 26 patients were ASST positive. Our study's mean duration of urticaria was 1.9 years, ranging from 2 months to 11 years. The difference in mean duration among ASST positive patients and ASST negative patients was not statistically significant.

A history of atopy was present only in 8 (8.48%) out of the 106 urticaria patients. Three patients with a history of atopy had ASST positivity, whereas five of those with a history of atopy were ASST negative. The difference in the proportion of ASST positivity in those with a history of atopy and those without a history of atopy was not statistically significant in our study.

Among 106 patients, 18 (16.9%) had abnormal thyroid function tests. Out of which 17 (94.4%) had hypothyroidism and 1 (5.6%) had hyperthyroidism. Among ASST positive patients, 10 had abnormal TFT, whereas in ASST negative patients, 8 had abnormal thyroid tests. There was no significant difference in the laboratory parameters in both ASST positive and Negative groups.

The difference in the proportion of ASST positivity in those with normal thyroid function tests and those with abnormal thyroid function tests was not statistically significant. In our study, ASST was positive in 39 patients (36.8%) and negative in 67 patients (63.2%).

There was no statistical difference in the gender and ASST results. Baseline urticaria activity score was comparable between ASST positive and negative groups (Table 1).

There was a significant fall in urticaria activity score in ASST positive (first week 15.3 to 10.8 in the ninth week) and ASST negative group (first week 16.2 to 9.2). There were no statistically significant falls in UAS in ASST positive and negative patients.

Hence, in our study, autologous serum therapy was equally effective in chronic urticaria patients irrespective of the ASST test (Table 2). Side effects reported in our studies were- 7 patients developed pain at the injection site, which lasted for 1.5 days (mean). No other side effects were reported in our study.

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**Table 1: Comparison between ASST positive and negative groups.**

| Variables | ASST positive (N=39) | ASST negative (N=67) |
|---|---|---|
| **Age (years)** | 23±8.4 | 24±9.6 |
| **Gender** | | |
| Males | 13 | 20 |
| Females | 26 | 47 |
| **Associated angioedema** | 8 | 13 |
| **Baseline UAS** | 15.3±6.4 | 16.2±7.2 |

**Table 2: ASST test results.**

| ASST result | Weeks UAS | | | | |
|---|---|---|---|---|---|
| | **Baseline** | **2** | **4** | **6** | **9** |
| **ASST positive (39 patients)** | 15.3 | 13.4 | 11.9 | 11.1 | 10.8 |
| **ASST negative (67 patients)** | 16.2 | 14.9 | 12.3 | 10.1 | 9.2 |

## DISCUSSION

Our study included one hundred and six consecutive patients with chronic urticaria above 18 years of age who attended the department of dermatology and venereology for one year. The prevalence of positive ASST in chronic urticaria patients and the clinical and laboratory parameters in ASST positive and ASST negative patients were studied. The effectiveness of AST in both ASST positive ASST negative patients was assessed. Chronic urticaria is a common disorder that affects 0.1% of the population.[11] Urticaria is a disabling condition and can prevent the patient from performing daily activities and has major detrimental effects on the quality of life. ASST was positive in 39(36.8%) of our patients. Results are comparable to the ASST positivity of 34% reported by Mamatha et al. 26.67% in a study by Godse et al in Mumbai.[12,13] ASST reflects the presence of functional autoantibodies.

Chronic urticaria has a significant effect on the patients' quality of life, and at times it is pretty challenging for the treating physicians. Chronic urticaria is usually managed with antihistamines, and if the disease is not responding, the dose of antihistamines is increased up to four times the standard dose. The adverse effects of antihistamines can interfere with daily activities. Moreover, after stopping the antihistamines, patients tend to relapse and will require counselling and restarting antihistamines among these patients. Also, there are few patients whose disease is not controlled with antihistamines and will need systemic steroids or immunosuppressive drugs regularly.

ASST is a novel therapeutic modality of treatment in chronic urticaria patients. It is postulated to act by inducing

anti-idiotypes (anti-idiotypes inhibit the function of disease-inducing antibodies) and shifting the Th2 cytokine profile to Th1. In our study, at least 60.8% ASST positive patients and 58 % ASST negative patients showed significant improvement in UAS during and after the treatment. the result is similar to initial studies published by Staubach et al and Bajaj et al where autologous whole blood and serum were used respectively in chronic urticaria patients.[14,15] in a study published by Staubach et al after eight weeks of intramuscular injection, there was decreased use of antihistamines and improved quality of life in the patients.[14] In a study done by Bajaj et al there was a significant improvement in the signs and symptom's and was sustained at least for 3-4 months after the last injections.[15] In contrast, a study done by Majid et al demonstrated that AST in ASST positive patients was not an effective treatment.[9]

In our patients, autologous serum was administered intramuscularly, and there was a significant fall in Urticaria activity score in ASST positive and ASST negative groups. In a study done by Godse et al autologous serum was injected subcutaneously, and at the end of 9 weeks, there was a significant fall in the UAS in the serum group.[16] SC injection offers the advantage of less pain, lesser chances of damage to nerves and blood vessels.

## CONCLUSION

Chronic urticaria has a significant effect on the patients' quality of life, and at times it is pretty challenging for the treating physicians. Oral antihistamines are the mainstay of the treatment, often on withdrawal causes relapse in the disease. Autologous serum therapy is a valuable adjunct for treating both ASST positive and negative patients chronic urticaria patients along with or without the standard treatments available as there are no dreaded side effects as it is the own patient's serum that is injected.

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