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Comparative study of effectiveness of autologous serum and histaglobulin in autologous serum skin test positive and negative cases of chronic urticaria

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Abstract:

AIMS AND OBJECTIVES: The aim of our study is to compare the effectiveness of autologous serum therapy (AST) with histaglobulin in patients of chronic urticaria.

MATERIALS AND METHODS: This was a prospective, comparative, randomized controlled, single-blinded study. Based on inclusion and exclusion criteria, patients were selected and divided into two groups by randomization. Autologous serum skin test was done in each patient irrespective of their groups. Group A ($n = 30$) received AST and Group B ($n = 30$) received histaglobulin. Patients' assessment was done every week for urticaria activity score (UAS) for 8 weeks.

STATISTICAL ANALYSIS: We used Mann–Whitney test to compare the means between two groups. Wilcoxon signed-rank test was used to compare pre- and posttreatment UAS scores.

RESULTS: Both therapies reduced UAS significantly ($P = 0.01$) at 8 weeks, and the reduction was observed every week. AST reduced UAS more than histaglobulin. However, within intergroup, difference was not significant. All patients had reduced severity of urticaria; however, complete remission (UAS = 0) was observed in three patients of Group A.

CONCLUSION: Group A (AST) showed statistically significant improvement than Group B (histaglobulin), but both showed a reduction in UAS with a longer treatment-free interval.

Keywords:

Autologous serum skin test, chronic urticaria, histaglobulin, serum

Introduction

Urticaria or hives (Latin “urtica” [to burn]) affects 0.5%–1% of the population at any given time.^[1] Patients of chronic urticaria suffer from irritable itch, waxing, and waning course and are also subjected to a huge antihistamine pill burden.^[2] Many studies compared the efficacy of various second-generation antihistamines as first-line treatment;^[3] however, their effectiveness is limited, so a modality that

can provide extended relief and reduce antihistaminic load needs to be researched upon.

Autologous serum and histaglobulin have been tried for various autoimmune diseases.^[4,5] Autoreactive urticaria is a subgroup of chronic urticaria containing circulating functional autoantibodies and routinely diagnosed by autologous serum skin test (ASST). Effectiveness of autologous serum therapy (AST) was determined in this subgroup.^[6,7]

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Hence, we carried out the study to assess the effectiveness and safety of AST and histaglobulin as an immunological therapy.

Materials and Methods

Study design

The study was designed as a single-center, single-blinded, randomized controlled trial of 12-month duration; patients (>18 years) of either sex suffering from chronic urticaria attending the dermatology outpatient department of a tertiary care center, Sir T. Hospital, were included after written informed consent from all participants after obtaining approval from the Institutional Ethics Committee.

Patient selection

The patients of chronic urticaria taken as in whom itching and wheals occurring daily or near daily (≥ 3 times/week) for ≥ 6 weeks and had moderate and severe urticaria score [Figure 1]. Pregnant and lactating women, patients taking immunosuppressant drugs, patients with severe renal and cardiac diseases, patients who were inability to come for weekly follow-ups, and patients with coagulation defects and acute allergic symptoms were excluded from the study.

Sample size calculation

The sample size was calculated by Epi Info software (Atlanta, Georgia). Totally 72 participants included in our study; among them, 12 not give consent, so we enrolled 60 patients.

Methodology

Patients were asked to discontinue any antihistamines 2 days before the test and at the start of the therapy. A thorough clinical examination was done to note any

associated comorbidity, and relevant investigations were done for their confirmation.

Patients were randomized into two treatment groups: Group A and Group B using a computer-generated random number table in 1:1 ratio. ASST was performed in all study participants, and the result was recorded after 30 min (as detailed below). The patients of Groups A and B received AST and injection histaglobulin, respectively. Patients in both treatment groups were instructed to consume tablet levocetirizine in an on-demand basis. Any participant experiencing intolerable symptoms of urticaria was instructed to contact the investigator.

Follow-up visits

At each successive weekly follow-up, AST or histaglobulin was given for 8 consecutive weeks. Injectable hydrocortisone and chlorpheniramine maleate were kept as rescue medications. At all these eight follow-ups, UAS was noted. After 8 weeks, therapy was discontinued, and the patients were followed up for improvement or recurrence of symptoms weekly for the next 24 weeks. Levocetirizine was administered throughout the study period in on-demand basis even after the completion of AST injections and histaglobulin.

Autologous serum skin test

Five milliliters of venous blood of the patient was drawn with a sterile, disposable syringe from the antecubital vein in sterile vacutainer for serum collection. The blood was subjected to centrifugation using centrifuge machine at the rate of 2000 rpm for 10 min at room temperature. About 0.05 ml of the serum was injected immediately intradermally into the patient's left flexor forearm 2 inches below the antecubital crease and 0.05 ml sterile normal saline as negative control into the right forearm using 31-G sterile disposable insulin syringe.



Figure 1: Wheals of urticaria



Figure 2: Positive autologous serum skin test

A reading of the wheal was taken after 30 min and at 1 h. Patients having wheal of ≥ 1.5 -mm diameter than that of controls with erythema were considered to be suffering from autoreactive urticaria (ASST positive) [Figure 2].

Group A – Autologous serum therapy

In Group A, 2 ml of the fresh serum separated from the patient's blood (as above) was given deep Intramuscular (IM) for 8 successive weeks.

Histaglobulin therapy

In another group, 1-ml subcutaneous injection of histaglobulin which is a combination of human normal immunoglobulin (12 mg) and histamine dihydrochloride (0.15 mcg) was given for 8 weeks.

UAS is calculated from the number and size of wheals, intensity of pruritus, duration of persistence of lesions, frequency of appearance of lesions, and frequency of antihistamine use, with each parameter having a score of 0–3, maximum score being 18.

Vital signs and adverse events were assessed at every week of follow-up. Laboratory test done for routine hemogram, total count differential count, hemoglobin percentage, liver function tests, serum urea, creatinine, viral markers, and C-reactive protein were recorded at baseline.

The primary end point was a reduction in UAS after 8 weeks of injection serum and histaglobulin. The proportion of patients who achieved complete remission at 24 weeks of therapy was noted. The baseline UAS was calculated as an average of daily scores for the 7 days at the screening visit. Similarly, during each visit, UAS was calculated as an average of daily scores for the preceding 7 days. Reduction in the requirement of antihistamine tablets was also noted.

Statistical analysis

Data were entered and analyzed using GraphPad software (California corp, USA). Mann–Whitney test was used to compare the means between two groups. Wilcoxon signed-rank test was used to compare pre- and posttreatment UAS scores.

Results

During the study period, a total of 72 patients were diagnosed with chronic urticaria, but 60 patients had completed the stipulated 8 weeks of treatment. They were divided into Group A and Group B after ASST. Demographic details are mentioned in Tables 1 and 2 and flowchart study [Figure 3].

Table 1: Baseline demographic data of the participants

Characteristics	Baseline values
Mean age (years)	31.3 $\pm$ 8.1
Female (%)	31 (51.7)
Male (%)	29 (48.3)
Urticaria with angioedema (%)	11 (18.3)
Urticaria without angioedema (%)	49 (81.6)
Mean duration (months)	7.1 $\pm$ 2.6

Table 2: Urticaria activity score and autologous serum skin test status in both groups

Characteristics	Baseline values
ASST status (%)	
Number of ASST-positive patients	16 (26.6)
Number of ASST-negative patients	44 (73.3)
UAS	
Mean UAS in total patients	12.4 $\pm$ 1.6
Mean UAS in Group A (serum)	12.3 $\pm$ 1.6
Mean UAS in Group B (histaglobulin)	12.6 $\pm$ 1.5

ASST=Autologous serum skin test, UAS=Urticaria activity score

Table 3: Reduction in number and urticaria activity score at baseline and 8 weeks in both groups

UAS	Group A		Group B	
	n (At baseline)	After 8 weeks	At baseline	After 8 weeks
Mild (0-6)	0	12	0	20
Moderate (7-12)	19	18	21	10
Severe (13-18)	11	0	9	0

UAS=Urticaria activity score

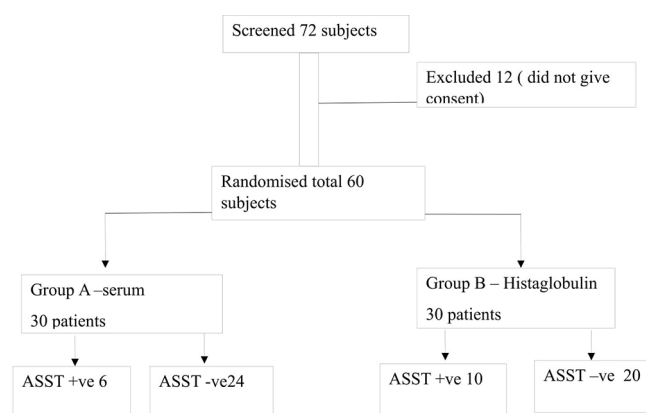


Figure 3: Flow chart of the study. UAS = Urticaria activity score, Group A = Serum, Group B = Histaglobulin

In patients of Group A, the efficacy end point was a mean reduction in UAS from 68.5% to 29% and in patients of Group B mean UAS value reduced from 69.4% to 39.4% by 8 weeks [Table 3].

We observed reduction in the UAS score during each week in both groups which was also found to be statistically significant by Dunn's multiple comparison test [Figure 4]. The onset of response was observed in the 2nd week in both groups, but it was clinically

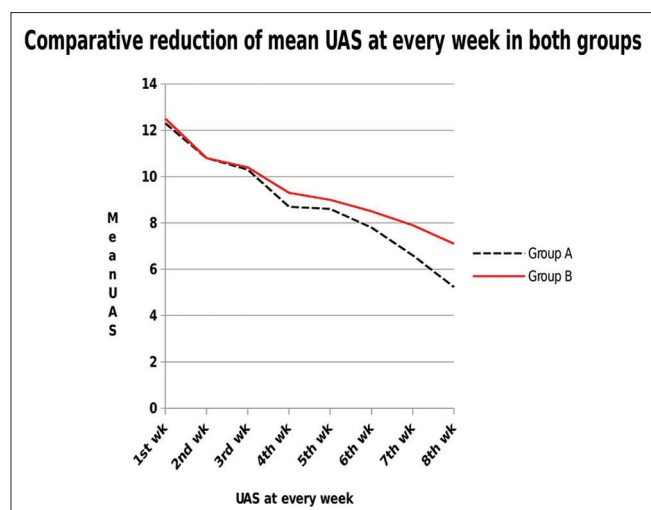


Figure 4: Weekly reduction of urticaria activity score in both groups

Table 4: Weekly reduction in urticaria score in group A (serum) and group B (histaglobulin)

UAS (n)	Mean UAS ($\pm$ SD)		P
	Serum	Histaglobulin	
UAS at 1 st visit (at start) (30)	12.3 $\pm$ 1.66	12.6 $\pm$ 1.5	0.9408
UAS at 1 st week (30)	12.3 $\pm$ 1.66	12.5 $\pm$ 1.62	0.9999
UAS at 2 nd week (30)	10.8 $\pm$ 1.08	10.8 $\pm$ 1.21	0.9999
UAS at 3 rd week (30)	10.3 $\pm$ 1.65	10.4 $\pm$ 1.08	0.8060
UAS at 4 th week (30)	8.7 $\pm$ 1.83	9.3 $\pm$ 1.44	0.2436
UAS at 5 th week (30)	8.6 $\pm$ 1.82	9 $\pm$ 1.36	0.1307
UAS at 6 th week (30)	7.8 $\pm$ 2.02	8.5 $\pm$ 1.60	0.1307
UAS at 7 th week (30)	6.6 $\pm$ 2.64	7.9 $\pm$ 1.77	0.0602
UAS at 8 th week (30)	5.23 $\pm$ 2.97	7.1 $\pm$ 2.77	0.0168 (significant)

UAS=Urticaria activity score, SD=Standard deviation

significant at the 4th week in Group A and 5th week in Group B.

Mean reduction in UAS in both groups was statistically significant at 8 weeks. The difference in response between these two groups was measured by Mann-Whitney test and considered statistically significant ($P = 0.0168$) [Table 4 and Figure 5].

ASST test was carried out in both groups prior to the study, and the mean reduction in UAS score among ASST-positive and ASST-negative cases is mentioned in Table 5.

Among 30 patients of Group A who completed therapy, complete remission (UAS = 0) was observed in three patients at 8 weeks and none in Group B. Excellent response ($\geq 75\%$ reduction) was observed in eight patients of serum therapy and two patients of histaglobulin therapy; good response (51%–74% reduction) was observed in eight patients of serum therapy and five patients of histaglobulin therapy; moderate response (25%–50% reduction)

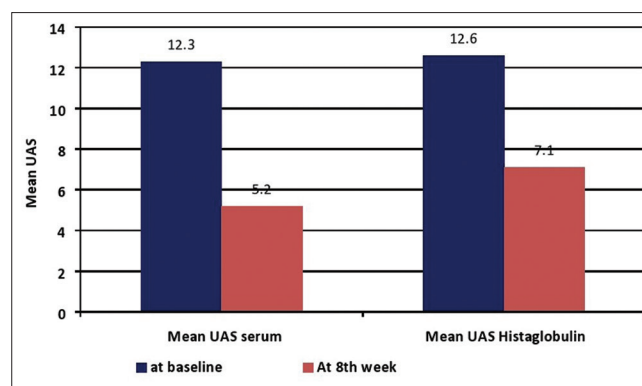


Figure 5: Mean reduction urticaria activity score at baseline and at 8 weeks

was observed in 11 patients of serum therapy and 16 patients of histaglobulin therapy; and poor response ($<25\%$ reduction) was observed in three patients of serum therapy and seven patients of histaglobulin therapy. During follow-up period, two patients of serum therapy had attained complete remission.

As mentioned in methods, we have enrolled patients with moderate and severe UAS score.

All patients in both groups enter into the mild and moderate score, and none of the patients remain in severe score; thus, improvement was observed in both groups [Table 3].

No life-threatening therapy-related adverse effect was noted either during or after the treatment in both groups. However, urticaria activity continued to remain at a low level among the study participants, and during follow-up period, three patients of Group A and six patients of Group B had a recurrence of the symptom.

Discussion

Chronic urticaria has endless clinical course and presentation and it was also troublesome for the patient. Treatment of chronic urticaria challenging task for the physician. In the pathogenesis of urticaria, mast cell degranulation plays a crucial role; however, the reason for degranulation is sometime unknown. In recent times, antibody to high-affinity IgE receptor (Fc ϵ RI) is identified and found to degranulate the mast cells by cross-linking the IgE receptors. This entity is known as autoreactive urticaria and it accounts for 27%–61% of chronic urticaria.^[6]

Second-generation antihistamines remain the mainstay of treatment. Even if it provides immediate relief from symptoms, it does not affect the immune pathogenesis.^[2] Different immunological agents that are being used are oral corticosteroids, cyclosporine, methotrexate, intravenous immunoglobulin, omalizumab, and tacrolimus.^[8,9] They

Table 5: Weekly comparison of autologous serum therapy and histaglobulin in autologous serum skin test positive and negative patients

Groups	UAS in ASST-positive patients of serum therapy	UAS in ASST-positive patients of histaglobulin therapy	P	UAS in ASST-negative patients of serum therapy	UAS in ASST-negative patients of histaglobulin therapy	P
Baseline score	12±2.757	12±0.81	0.9999	12.4±1.34	12.9±1.80	0.4273
1 st week	12±2.7	11.9±0.7	0.9135	12.4±1.34	12.8±1.9	0.5383
2 nd week	10.5±1.76	10.8±1.31	0.7026	11±0.8	10.85±1.22	0.9528
3 rd week	10±2.28	10.2±0.91	0.4564	10.4±1.5	10.6±1.18	0.9905
4 th week	8.83±2.78	9.8±1.54	0.4153	8.75±1.59	9.05±1.39	0.5524
5 th week	8.8±2.78	9.4±1.57	0.6080	8.58±1.58	8.8±1.28	0.6613
6 th week	8.5±2.8	9±1.63	0.6613	7.62±1.78	8.3±1.62	0.2019
7 th week	6.8±4.0	8.3±2.0	0.3464	6.62±2.28	7.7±1.72	0.1107
8 th week	6.5±3.7	8.1±2.02	0.2800	4.91±2.76	6.6±2.32	0.044 (significant)

ASST=Autologous serum skin test, UAS=Urticaria activity score

Table 6: Comparison of various immunotherapies with the present study

Source	Tseng <i>et al.</i>	Bajaj <i>et al.</i>	Rajesh G <i>et al.</i>	Comparative present study	Comparative present study
Intervention	Autologous whole blood - weekly subcutaneous injection	Autologous serum therapy - weekly IM injection	Injection histaglobulin subcutaneous weekly	Autologous serum therapy - weekly IM injection	Injection histaglobulin subcutaneous weekly
Duration of treatment (weeks)	8	9	8	8	8
Type of study	Retrospective review	RCT	Prospective Clinical study	RCT	RCT
Onset of action	NA	NA	1 st week	2 nd week	2 nd week
Treatment response	11/20 patients responded	UAS reduced by 54% in ASST-positive patients and 24% in ASST-negative patients	UAS reduced by 80% 45% showed complete remission	UAS reduced by 45.8% in ASST-positive patients and 60.4% in ASST-negative patients	UAS reduced by 32.5% in ASST-positive patients and 45% in ASST-negative patients
Follow-up duration (weeks)	24	24	24	24	24
Relapse rate	NA	NA	2/14 responders	3/30 responders	6/30 responders
Side effects	Nil	Nil	Nil	4/30 patients had developed wheals after injection	Nil

NA=Not available, ASST=Autologous serum skin test, UAS=Urticaria activity score, RCT=Randomized controlled trial, IM=Intramuscular

act by preventing antibody formation thereby decrease degranulation. There were few studies which used these drugs, but the cost of this drugs and side effects makes its utility limited.^[1]

AST and histaglobulin both are immunological treatment, so thinking of this basic mechanism, we chose to use autologous serum and histaglobulin as therapeutic methods.

In this study, AST group shows a better reduction in UAS than histaglobulin group and reduces the burden of antihistamines.

We could not find the use of these two modalities in a single study after searching PubMed, Google Scholar, and ScienceDirect.

Table 6 shows a comparison of different immunological agents with the present study.

In case of serum therapy, a study by Bajaj *et al.* shows a mean reduction in UAS more in ASST-positive patients whereas we found a mean reduction in UAS more in ASST-negative patients.^[4] However, we have fewer ASST-positive patients (6 out of 30) who were in serum group. In few studies, they took follow-up period up to 2 years in our study, and we have only follow-up period of 16 weeks. During that, few patients were a dropout and three patients relapsed after 1 month of treatment in Group A.

Previously, whole blood therapy is used for many autoimmune diseases such as pemphigus, severe dry eye (Sjogren's syndrome and rheumatoid arthritis), cancer, and allergic disease like atopic dermatitis.^[10]

Tseng *et al.* who used whole blood as therapy in chronic urticaria reported minor side effects such as bruising and soreness at injection site and also few patients developed worsening of symptom at the end than baseline.^[11,12] We did not notice any above similar complaint in our

patients, but four patients developed wheals after the injection.

The autologous serum has circulating autoreactive factor and is given by fine needle to reduce injection site pain in contrast to whole blood in which the above factor is absent and injections are more painful. The mechanism by AST works in pemphigus by inhibiting disease inducing antibodies and also shifts Th2 cytokine profile to Th1 in urticaria. Bajaj *et al.* used the serum as a modification of whole blood therapy in chronic urticaria. Godse *et al.* used serum as subcutaneous injection.^[13]

Histaglobulin is capable of eliciting an immunological response with the production of highly potent antihistaminic antibodies. The antihistamine antibodies formed will neutralize the released histamine and eliminate urticaria effectively.^[14]

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

Rajesh *et al.* showed a marked reduction in UAS (80%) and complete remission (45%) in patients of receiving histaglobulin injection.^[5] Our figure was very lower than their result. However, these two studies are not easily comparable as they did not divide patients into ASST-positive and ASST-negative group. In our study, during follow-up period, six patients develop relapse within 3–4 weeks after the treatment in Group B.

Histaglobulin has been widely used in the treatment of allergic rhinitis and in various allergic disorders such as asthma, atopic dermatitis, chronic urticaria (CU), erythema multiforme, and cutaneous drug allergy.

In our study, we found a good response in both groups irrespective of their ASST status; this raised the question about the plausibility of ASST as a reliable test to detect autoreactive urticaria. Positive ASST was also found in a normal individual, a person having *Helicobacter pylori* antibodies and person sensitive to non steroidal anti-inflammatory drugs.^[7] Hence, we needed another test in the future for research of autoreactive urticaria.

Our study emphasizes that AST is cost-effective and useful alternative to other treatment modalities and also

gives longer treatment-free interval as AST has a low relapse rate compared to histaglobulin. ASST-negative patients also showed an effective result with both treatments.

Limitation

In this study, we have a small sample size and thus less number of ASST-positive patients in Group A. Due to randomization, they fall unevenly in both groups, so our result was affected by that figure. There was also dropout of participants on follow-up period.

Conclusion

Patients of chronic urticaria get more relief during treatment and it has long-term treatment-free period too. No adverse effects were noted with any of the drugs. They both can be used as an alternative to the immunosuppressive agents. We also noted patient satisfaction with this type of therapeutic modalities.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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