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The Effect of Autologous Serum Therapy on Disease Severity in Patients with Chronic Urticaria

Farhad Abolnezhadian[1,2], Soheila Alyasin[1,3], Reza Amin[1], and Maryam Babaei[1]

[1] Allergy Research Center, Division of Immunology and Allergy, Nemazee Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Department of Pediatrics, Abuzar Children's Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Pediatrics, Division of Immunology and Allergy, Nemazee Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Limited evidence has been obtained concerning the beneficial effects of autologous serum therapy in treatment of skin disorders particularly chronic urticaria. In the present study, we have assessed the effect of this treatment method in patients with chronic urticaria (CU).

This randomized single-blind controlled trial was performed on fifty consecutive patients with chronic urticaria. The patients were randomly assigned to receive autologous serum (as the case group, n=35) or normal saline (as the control group, n=15) and treated with monthly autologous serum therapy or normal saline for 6 months. The considered study endpoint was changes in total severity score (TSS) at the 6 months follow-up visit. The TSS score was assessed at baseline as well as at the ninth week and the sixth month of interventions.

The mean±SD of TSS at the ninth week of intervention was 10.94±3.92 in autologous serum therapy group and 11.67±2.72 in the normal saline group (p=0.458). Furthermore, the mean values of TSS at the sixth month of treatment in the study groups were 8.29±6.29 and 9.27±4.89 respectively (p=0.593). A downward trend in TSS, from baseline to the end of treatment, was seen in the case and control groups (p<0.001 for both), however the trend of this decline was insignificant between the two groups (p=0.592). The change in the trend of TSS after 6 months of treatment was independent from the administration of autologous serum when compared with normal saline administration (beta=-0.962, p=0.630). Multivariate linear regression model with the presence of baseline factors including gender, age, disease duration and history of atopy was performed to assess difference in TSS at six-month follow-up visit compared with the baseline value. Only young age was associated with more reduction of TSS (beta=0.163, p=0.023).

We found no difference in the effects of autologous serum therapy and normal saline on the trend of the changes in disease severity in patients with chronic urticaria.

Keywords: Angioedema; Antihistamines; Urticaria

Corresponding Author: Soheila Alyasin, MD;
Department of Pediatrics, Division of Immunology and Allergy, Shiraz University of Medical Sciences, Shiraz, Iran, Tel: (+98 912) 5154 816, Fax: (+98 711) 6474 326, E-mail: alyasins@sums.ac.ir

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INTRODUCTION

Chronic urticaria, is characterized by persistent wheals or hives, and frequently originates from degranulation of cutaneous mast cells leading to extravasation of plasma in the dermis layer.[1] This clinical cutaneous disorder may have an idiopathic pattern or may appear secondary to other underlying conditions such as drug reactions, physical pressure, sun exposure, fibromyalgia, reactive autoimmune responses, arthropod bites or stings, some viral and bacterial infections, psychological factors, or even food allergy.[2-6] Chronic urticaria is an irritating cutaneous disease affecting daily living activities and quality of life and carries heavy healthcare costs. Some studies have been even analogized the disease load similar to those with chronic cardiovascular disorders.[7]

A combination of antihistamines, anti-inflammatory drugs, immuno-suppressants, monoclonal antibodies directed to immunoglobulin E, antibiotics, and antidepressants have been introduced as the main treatment regimens for chronic urticarial.[8-10] Along with these medications, avoiding mental distresses, identifying triggering risk factors, and using some cutaneous lotions containing menthol and phenol can be helpful to relieve symptoms of the disease, however these treatment strategies are not definitive treatment methods.[11]

Autologous Serum Therapy (AST) has been proposed as a treatment for a variety of diseases such as allergic, inflammatory, infectious, and autoimmune disorders.[13] The main mechanism of AST is tolerisation and desensitization of the affected patients to pro-inflammatory signals expressed in circulation system.[14] One of the main advantages of this therapeutic method is related to its cost-effectiveness. Limited evidence has been obtained concerning the beneficial effects of AST in treatment of skin disorders particularly chronic urticaria.[15-17] More trials are needed to confirm its effect on symptoms' relief in patients with chronic urticaria. We aimed to assess the effect of AST injection in patients with chronic urticaria.

MATERIALS AND METHODS

Study Population

This randomized single-blind controlled trial was performed on 50 consecutive patients with chronic urticaria referred to the Allergy clinic of Shiraz University of Medical Sciences from January 2013 to January 2014. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (CT-P-9367-6837). Moreover, written informed consent was obtained from all participants.

The inclusion criteria were the presence of severe chronic urticarial lasing for at least 6 weeks and most days of the week and lack of response to treatment with antihistamine. A history of serious systemic diseases, positive food allergy skin test, urticarial vasculitis, pregnancy or breast feeding, alcohol use, or using immunosuppressive drugs were all considered as the exclusion criteria. As initial assessment, all patients underwent a variety of laboratory parameters' testing including blood cell count, tests of thyroid function, liver function, anti-nuclear anti body (ANA), anti thyro-proxidase (Anti TPO), anti-thyroglobulin, stool exam, and urine analysis. If taking second-generation antihistamines for five days or first-generation antihistamines for two days, the patients were asked to avoid using the drugs two days before the first visit. Upon the initial visit, all patients were examined physically and the results of laboratory analyses were checked. Also, baseline characteristics and medical history (including duration of disease, history of physical urticaria, history of atopy, or presence of angioedema) were recorded by interview.

Study Intervention

At first visit, serum was separated by centrifuging the patients' blood at 2000 rpm for 10 minutes and 0.05 ml of autologous serum, 0.05 ml of normal saline as the negative control and 10 µg/ml of histamine as the positive control were injected intradermally at least 5 cm apart on the volar aspect of the left forearm. A 31-gauge needle was used for injections. Sites of whealing in the past 24 hours were avoided and the results were read after 30 minutes.

Regardless of the autologous serum skin test (ASST) condition, the patients were randomly assigned to receive autologous serum (as the case group) or normal saline (as the control group). For autologous serum therapy, 6 ml blood was drawn, the serum was separated and a 2.5 ml deep intramuscular injection was given in the deltoid muscle. Rescue antihistamine was permitted in the run-in period; no other drugs were permitted. However, the patients were allowed to use only cetirizine if necessary with a minimum and maximum dose of 10 and 40 mg. The treatment was

continued weekly for 9 weeks and then monthly for 6 months. At baseline and at the end of the ninth week, total severity score (TSS) was assessed. Then, the patients were treated with monthly autologous serum therapy or normal saline for 6 months and TSS was reassessed. Rescue antihistamine was permitted as in the run-in period; no other drugs were permitted. In each visit, the patients asked for probable drug-induced side effects. Six separate parameters of disease activity and severity were recorded on a 0-3 scale at baseline (0 week), end of treatment (9 weeks) and follow-up (6 months). Based on these, a 0-18 TSS was generated and overall disease severity was classified as clear (TSS=0), mild (TSS=1-6), moderate (TSS=7-12) or severe (TSS=13-18).[18] ASST was considered positive when the average of two perpendicular diameters of the autologous serum wheal was ≥1.5 mm more than the normal saline wheal. In this study, the considered study endpoint was changes in TSS at the end of the 6-month follow-up period.

Statistical Analysis

The multivariate linear regression analysis was used to determine the effect of autologous serum injection on severity of chronic urticaria with the presence of baseline variables including gender, age, disease duration and history of atopy. Trend of the changes in TSS within 6 months of follow up was assessed using ANOVA test on repeated measures. Mann-Whitney and Chi-square tests were used as appropriated. Data were analyzed using SPSS software, version 20. $p<0.05$ was considered statistically significant.

RESULTS

One of the patients, who received autologous serum, discontinued and thus was excluded from the study. Finally, 35 patients in case group and 15 patients in control group were assessed (Figure 1). Baseline characteristics of study patients are summarized in Table 1. The mean±SD of patients age was 34.80±13.15 and 37.87±10.58 years in the case and control groups, respectively (p=0.429). Regarding gender distribution, 11.4% and 40.0% of the patients in case and control groups were men, respectively. The mean ± SD of disease duration was 3.60±3.50 and 4.53±3.93 years in case and control groups, respectively (p=0.442). A positive history of atopy in the forms of asthma (14.3%), allergic rhinitis (17.1%), and drug-induced allergy (2.9%) was present in the case group. The corresponding figures were 6.7%, 6.7%, and 0.0%, respectively in the control group with no difference across the two groups. History of physical urticaria was 85.7% and 66.7%, respectively, in the case and control groups (p=0.143), and the presence of angioedema was observed in 77.1% and 93.3% of the patients in the case and control groups, respectively (p=0.247).

Regarding baseline Para clinical examinations, liver function test was normal in all subjects. All patients in both groups had negative stool exam test. Abnormal thyroid function test was seen only in one patient receiving normal saline and abnormal urine exam test was found only in a patient receiving autologous serum treatment.

With respect to the results of TSS at different study time points, the mean ± SD baseline TSS in the case group and normal saline group was 16.20 ±1.49 and 16.00±1.19, respectively with no significant difference between the two groups (p=0.648). All participants had severe urticaria on admission with TSS ranging from 12 to 18. The mean±SD TSS at the 9th week of interventions was 10.94±3.92 in the case group and 11.67±2.72 in the control group (p=0.458). Furthermore, the mean±SD TSS at the sixth month of treatment was 8.29±6.29 and 9.27±4.89, respectively with no difference between the two groups (p=0.593).

A downward trend in TSS from baseline to the end of treatment was seen in the case and control groups ($p<0.001$ for both repeated-measure ANOVA test), However, the trend of this fall was insignificant between the two groups (p=0.592). The frequency of mild, moderate and severe urticaria at ninth weeks was 11.4%, 57.1%, and 31.4% in the case group and 0.0%, 66.7%, and 33.3% in the control group, respectively (p=0.390). Moreover, at 6 months, the signs of urticaria were cleared in 25.7% of patients received autologous serum and also in 13.3% of those who received normal saline, while mild, moderate, and severe urticaria remained observable in 11.4%, 34.3%, and 28.6% of patients in the case group and in 6.7%, 46.7%, and 33.3% in the control group, respectively (p=0.689).

Considering difference in TSS at the 6 months follow-up visit compared to baseline value and using the multivariate linear regression model with the presence of baseline factors including gender, age, disease duration and history of atopy (Table1), the change in the trend of TSS after 6 months of treatment

Table 1. Multivariate linear regression analysis to compare effect of autologous serum compared to normal saline in urticarial patients

Variable	Unstandardized Coefficients		Sig.
	B	Std. Error	*P*=values
(Constant)	-17.343	3.623	<0.001
Treatment group	-0.962	1.983	0.630
Male gender	0.287	2.339	0.903
Age	0.163	0.069	0.023
Disease duration	-0.021	0.229	0.926
Asthma	0.778	2.411	0.749
Allergic rhinitis	4.148	2.462	0.100
Drug-induced allergy	4.687	5.679	0.414
Physical urticaria	0.561	2.423	0.818
Angioedema	4.000	2.160	0.072

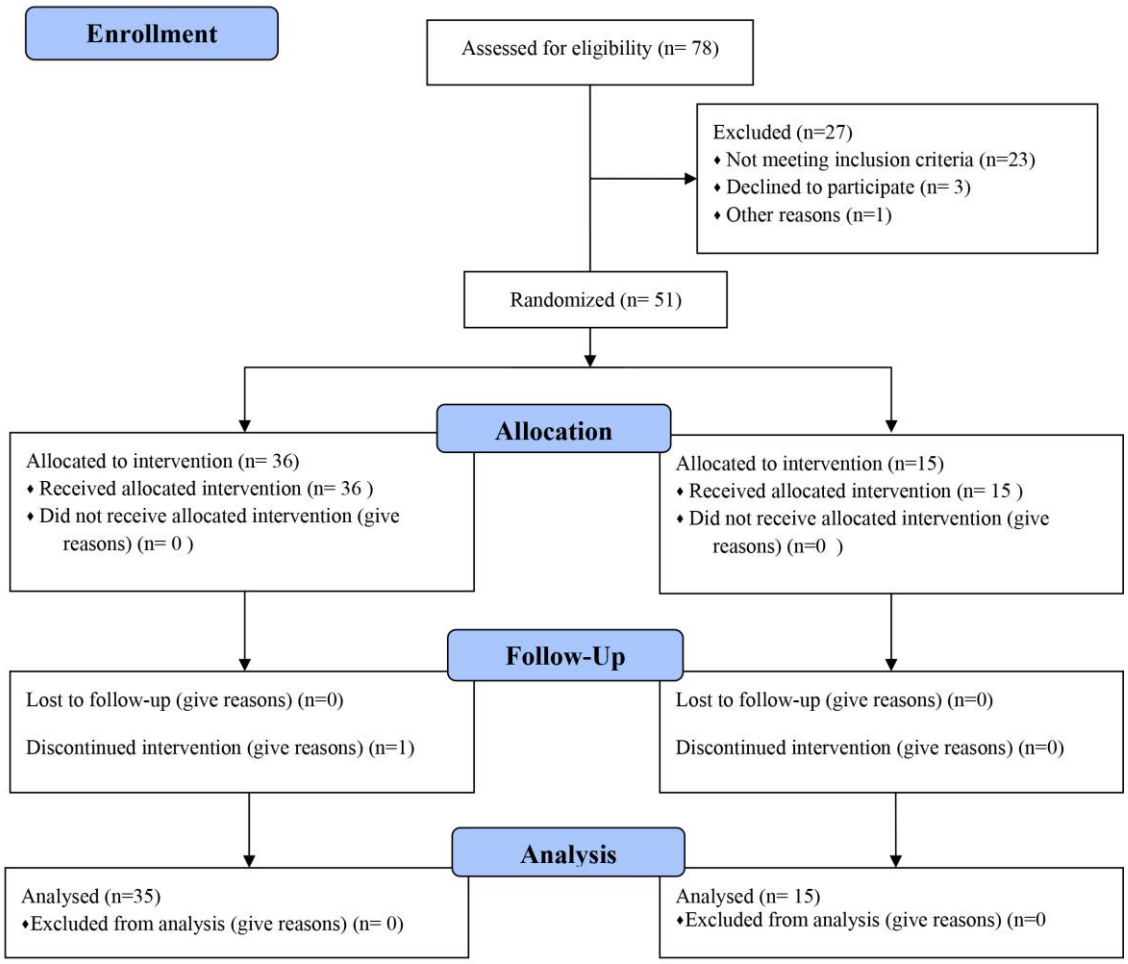

Figure1. Flow diagram of included and excluded patients in our study.

was independent from the use of autologous serum when compared to normal saline administration (beta=-0.962, p=0.630). The trend of the changes in TSS in case and control groups within 6 months of follow-upwas determined and only young age was associated with more reduction of TSS (beta=0.163, p=0.023).

DISCUSSION

Increased level of circulatory autoantibodies such as anti-IgE plays a major role in the onset of symptoms in chronic urticaria. Systematic circulation of these antibodies can induce release of histamine from mast cells and basophils.[19,20] 30-40% of patients with chronic urticaria have histamine-releasing auto-antibodies directed against the high-affinity IgE receptor and approximately 27-61% of these patients have these antibodies in their circulation.[21,22] The use of auto-hemotherapy as injecting the patients' own blood and AST can be effective on ameliorating symptoms of chronic urticaria. Consistent with previous trials, we attempted to assess the effects of AST on the severity of chronic urticaria. The patients were scheduled for long-term treatment with autologous serum and then followed to assess the trend of changes at three study time points.

We found that patients receiving autologous serum had a downward trend of TSS within 6 months of follow-up. However, a similar trend was also observed in the control group who had received normal saline. On the other hand, no difference was found between the therapeutic effects of autologous serum and normal saline in decreasing disease severity. Although, at the beginning of study, all patients suffered from severe chronic urticaria, a notable number of patients in both groups returned to a normal state without additional treatment.

Considering the probable confounding effects of some baseline factors such as sex, age, duration of disease, and previous history of atopy, on therapeutic effects of autologous serum, we adjusted our obtained results for these underlying factors which turned out to no differences between the two treatment methods (autologous serum and normal saline) in relieving symptoms of urticaria.

In a trial by Bajaj and colleagues,[18] improved symptoms of chronic urticaria were seen in 24.2% and 23.0% of patients with positive and negative ASST, respectively. In a study by Staubach et al,[23] AST treatment led to improved disease symptoms and its severity, as well as improved level of quality of life. Majid et al[16] showed that about two-third of patients did not demonstrate any significant reduction in TSS at the end of the treatment period. Debbarman et al,[15] showed more improvement in AST group when compared with placebo group in TSS within 8 weeks of follow-up.

In our observation, older patients experienced delayed improvement in disease severity indicated by falling TSS. Some studies could show higher rate of atopy and also higher prevalence of acute dermatitis in the elderly with chronic urticaria[24]. With the presence of underlying risk profile and simultaneous comorbidities in older patients, the trend of the disease remission slows down.

One of the limitations of our study was that the number of patients in the control group was less than that of the case group which might have affected our results. Another limitation was that our control group received placebo which might affect the interpretation of results since we did not have a group receiving a routine treatment modality. Our study showed similar downward trend of declining disease severity following AST treatment method and normal saline administration as the placebo, indicated by TSS.

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