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Autologus Serum Therapy Efficacy as Adjunctive Treatment to Antihistaminics in Chronic Spontaneous Urticaria Patients

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Abstract

Background: Chronic urticarial patients suffer from recurrent wheals which are severely itching for more than 6 weeks. The symptoms are more in auto-reactive urticaria (arCU) where auto-antibodies in blood flares-up the condition.

Autologus serum skin test (ASST) is regarded of a great value in the primary assessment of patients' auto reactivity. Autologous serum therapy (AST) is a promising treatment modality for CSU patients with positive ASST by inducing desensitization to the pro-inflammatory mediators expressed in their blood.

Aim of the work: Improvement of chronic urticarial symptoms with a therapeutic option that is cheaper, safer and less risky than standard treatment options.

Patients and methods: Single-blind randomized controlled clinical trial study was done on 48 CU patients (+ASST) and randomized into 2 groups; 24patients in cases group on anti-histamines will receive 9 weekly injections of AST and another 24 patients in control group will receive antihistamines alone for 9 weeks. We compared the urticarial activity score-7 of both groups at baseline,

fourth week, ninth week of treatment and at twelfth week of follow up after treatment to evaluate the efficacy of addition of AST to conventional treatment with antihistamines.

Results: The mean of UAS-7 was decreased in both treatment groups throughout the twelve weeks of treatment and follow up but the UAS-7 showed significant decrease in the cases group more than that of the control group from the fourth week onwards as $P< 0.05$.

Conclusion: In patients with arCU, AST is a useful adjunct to antihistamines which improves the urticarial symptoms.

Keywords: Chronic spontaneous urticaria, Autologous serum skin test, autoreactive urticarial, autologous serum therapy, chronic spontaneous urticaria.

Introduction

Patients with Chronic urticaria (CU) suffer from recurrent development of wheals which are severely itching and sometimes, these wheals are accompanied by angioedema lasting for more than 6 weeks, this condition occurs spontaneously in 80-90% of CU patients and is called chronic spontaneous urticaria (CSU) [(1)]. In 40-50% of CSU, there is evidence that IgG auto-antibodies to the alpha subunit of the Fc receptor of IgE molecule which is anti-FceR or, anti-IgE auto-antibodies can activate basophils to release histamine (2). Autologus serum skin test (ASST) is a skin reaction of erythematous and/or wheal-type in response to the autologous serum which indicates the presence of autoantibodies, which may be responsible for the mast cells degranulation [(3)]. Standard treatment of CSU is directed towards symptom control by second generation antihistamines against the H1 receptors but only 40% of those patients experienced complete clearing of their symptoms (4). Options for refractory CSU as immunosuppressive agents as (corticosteroids, cyclosporine), methotrexate and omalizumab are limited by factors like need for prolonged therapy, fatal side effects, presence of associated disorders, need for continous

laboratory testing, regular patient monitoring, and high cost of therapy [5]. Autologous serum therapy (AST) is a promising treatment modality for CSU patients with positive ASST by inducing tolerisation or desensitization to the pro-inflammatory mediators expressed in their blood [6].

Patients and Methods

The study was a single-blind randomized controlled clinical trial done between January and May 2015. During the study period, seventy-four patients with CSU who attended the Allergy outpatient clinic, Dermatology outpatient clinic at SCUH and El-Sheikh Zaid Dermatology Clinic were included in our study after obtaining approval of Local Research Ethics Committee and written informed consent was taken from each one of study participants. Patients who were less than 12 years, pregnant, lactating mothers, suffering from immunosuppression due to drug or disease, hepatitis B or C patients were not included in our study. A detailed history and physical examination were done for all the patients. All patients were asked to stop antihistamines 2 days before the ASST test was done on all the 74 patients. Only 48 patients who were ASST+ve patients were only included in this study.

Autologus serum skin test (ASST):

Five milliliters venous blood was taken from all patients by using sterile 27-gauge 10-ml syringes. The blood samples were placed in glass tubes without anticoagulants. Collected venous blood was stored at room temperature for 30 minutes and subsequently centrifuged for 10 minutes at 3000 rpm. After cleansing areas of both forearm, 0.05 ml of physiologic saline (as negative control) and 0.05 ml of autologous serum were injected 5 cm apart on the right forearmand another intradermal injection of 0.05 ml histamine on the left forearm (as a positive control) to create a papule to prevent interference between the erythemas and swellings caused by the autologous serum and histamine.

The injection was considered to have been administered too deep, If a papule was not observed after the injection, and should be repeated after 2 days. After 30 minutes, the results were evaluated. The interpretation of results was done by measuring the swelling diameter as the mean between the widest diameter and perpendicular diameter. If the diameter of swelling resulting from the autologous serum exceeded that from physiologic saline injection by 1.5 mm, the swelling was defined as positive.

The test result was considered negative, if there were erythema without swelling, so that the test should be repeated after another 30 minutes. If there was no reaction at all after 60 minutes, the test was evaluated as negative [(7)].

Forty-eight patients were enrolled in the study and randomized by computer generated random numbers into two groups: cases group (AST group) who were 24 CSU patients and treated with 9 deep intramuscular gluteal injection of autologous serum once weekly in addition to their conventional treatment with antihistamines (cetirizine 10 mg) and control group (conventional therapy group) who were 24 CSU patients and treated with conventional therapy with oral H1 antihistamines only (cetirizine 10 mg).

Autologous serum therapy:

Five ml venous blood of the patient was drawn with a sterile, disposable syringe from the antecubital vein, then blood was centrifuged for 10 min (3000 rpm), and 2 ml of the serum was injected deep intramuscularly into the gluteus muscle with a 27G needle. The procedure was repeated for 8 weeks [(8)].

Effectiveness parameters:

The primary outcome measures for effectiveness were Urticaria activity score-7. UAS is used widely in patients with CSU that includes 2 items: number of hives and intensity of pruritus. Items were scored individually, and the UAS-7 was

calculated as the sum of pruritus intensity and number of hives over 1 week before the day of blood sampling. Patients themselves documented a 24-h self-evaluation scores for 7 days applying the following scheme: no wheals = 0, <20 wheals/24 h = 1, 20-50 wheals/24 h = 2, >50 wheals/24 h = 3 and pruritus intensity: no = 0, mild = 1, moderate = 2, severe = 3. Weekly UAS equals the sum score of 7 consecutive days with a minimum score of 0 and a maximum score of 42. Consequently, weekly UAS will be graded as follows: 0-14 (mild), 15-29 (moderate) and 30-42 (severe) [(9)].

Safety parameters:

Specialized staff of the Allergy and Immunology should observe AST. Department with a period of half an hour to observe any complications as swelling, difficulty in breathing, nausea or signs of shock as hypotension taking all the required precautions by preparing two ampoules of adrenaline 1 mg/ml, and one ampoule of antihistamines as promethazine or diphenhydramine. Sterile injection technique is recommended. Proper labeling and injection technique were advised to avoid infection transfer.

Statistical analysis:

Statistical analysis: All the grouped data was statistically evaluated using SPSS (statistical package for social sciences) program (windows version number 11). All values were presented as means +/- SD. Data derived from the two groups were evaluated by one - way analysis of variance (ANOVA). Difference between two groups was compared by Mann-Whitney U Test. Data was considered statistically significant with a P value < 0.05.

Results

Among 74 study participants, 48 were randomized equally into two groups. In this study, females outnumbered males in both groups as in cases group 4% of

patients were males and 96% were females, while in control group 8.3% were males and 91.6% were females. The age was comparable in both cases and control groups as ranged from 18 to 44 years in cases group with mean of 32.6 years and from 14 to 42 years in control group with mean of 32.6 years. The disease duration was comparable between cases and control groups as was ranged from 4 months to10 years in cases with mean of 4.4years, while in control group was ranged between 6 months to12 years with mean of 4.5years. UAS was comparable at baseline, and decreased in both groups. However; intergroup comparison revealed that the decrease was significantly more in the AST group from 4 th follow-up and was evident till end of follow up**.** At baseline, there was no significant statistical difference in total UAS-7 score between the both treatment groups, where the mean of UAS-7 for cases group was 36.7 and the control group was 34.5**.** At the 4th week, the mean of UAS-7 of cases group was decreased from 36.7 at baseline to become 17.1 at the 4th week. But in the control group, the mean of UAS-7 was decreased from 34.5 at baseline to become 28.6 at the fourth week. At the ninth week, there was significant statistical difference in UAS-7 mean between both groups as the mean of UAS-7 of cases group was 10.2. But in the control group, the mean of UAS-7 was 21.1. After 12 weeks from completion of treatment, the mean of UAS-7 remained decreasing in the cases group to reach 8.8, so they showed tolerance even after discontinuation of injection. But in the control group, the mean of total UAS-7 was 16.4. To clarify the influence of adding AST to antihistamines in cases group, we compared the mean of UAS-7 throughout the weeks of treatment and follow up and we founded significant decline in UAS-7 accompanied by significant improvement in urticarial symptoms at the fourth week compared to baseline, at the ninth week compared to the fourth week and at the twelfth week compared to the ninth week.

On the contrary, the control group who received antihistamines only and by comparing the mean of UAS-7 throughout the weeks of treatment, we founded no significant decline in UAS-7 throughout the weeks of treatment and follow up except at the 9th week as compared to the 4th week.

Tables and Figures:

Table 1: Demographic data of the studied groups regarding age, urticarial duration, sex, residence and education level.

	Cases group (24)	**Control group (24)**	**P value**
Age (years)			
Mean ± SD	32.6±8.3	32.6±8.3	1.000
Range	18-44	14-42	
Urticaria duration (years)			
Mean ± SD	4.4±5.9	4.5±6.6	0.850
Range	0.33-10	0.5-12	
Gender (%)			
Males	1 (4%)	2 (8.3%)	0.283
Females	23 (96%)	22 (91.6%)	

Table 2: Comparison between the mean of UAS-7 of the two studied groups through weeks of treatment and follow up.

	Cases group (24)	**Control group (24)**	**P value**
Age (years)			
Mean ± SD	32.6±8.3	32.6±8.3	1.000
Range	18-44	14-42	
Urticaria duration (years)			
Mean ± SD	4.4±5.9	4.5±6.6	0.850
Range	0.33-10	0.5-12	
Gender (%)			
Males	1 (4%)	2 (8.3%)	0.283
Females	23 (96%)	22 (91.6%)	
Residence (%)			
Urban	7 (30%)	11 (45%)	0.176
Rural	17 (70%)	13 (55%)	
Educational level (%)			0.076
Literate	5 (22.2%)	10 (40.35%)	
Illiterate	19 (77.8%)	14 (59.65%)	

Figure 1: Comparison between the mean of UAS-7 of the two studied groups through weeks of treatment and follow up**.**

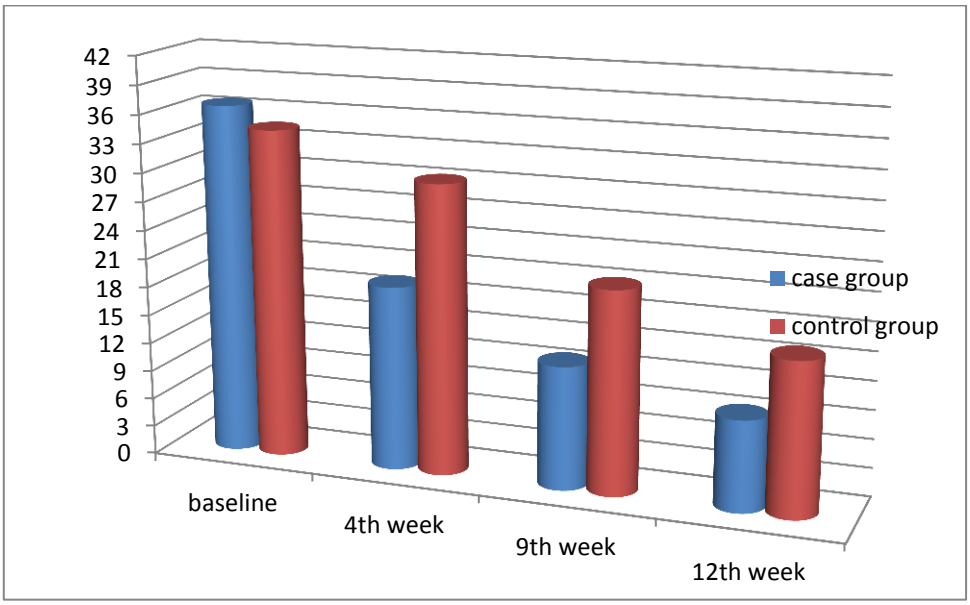


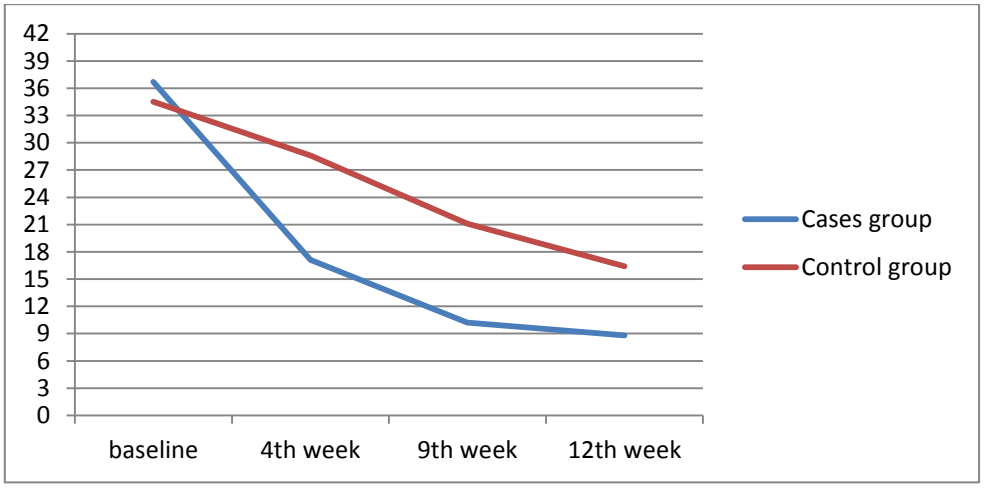
Table 3: Differences in mean UAS-7 throughout weeks of treatment of cases group

	Cases group (24)	**P value of mean difference**
Baseline UAS-7 Mean ± SD	36.7±8.7	
4th week UAS-7 Mean ± SD	17.1±14.9	**<0.001***
9th week UAS-7 Mean ± SD	10.2±16.7	**0.003***
12th week UAS_7 Mean ± SD	8.8±14.4	**0.003***

Table 4: Differences in mean UAS-7 throughout weeks of treatment of control group

	Cases group (24)	**P value of mean difference**
Baseline UAS-7 Mean ± SD	36.7±8.7	
4th week UAS-7 Mean ± SD	17.1±14.9	**<0.001***
9th week UAS-7 Mean ± SD	10.2±16.7	**0.003***
12th week UAS_7 Mean ± SD	8.8±14.4	**0.003***

Figure 2: Comparison between the mean of UAS-7 of the two studied groups through weeks of treatment and follow up**.**



Discussion

CU is a common problem and negatively affects both social life and work negatively because of its chronic annoying course and poor therapy response.

Today, we know that up to 50% of CU may be arCU (10). ASST is an in vivo test that assesses auto reactivity in arCU patients, particularly during the active phases of the disease (11). The pharmacotherapy for urticaria depends on two important modes of action; the first is to neutralize the effect of products of degranulation and the other is to prevent degranulation.

Antihistamines and leukotriene inhibitors, are the mainstay for urticaria management but sometimes, they are insufficient in controlling urticaria. So we have to use immunosuppressive agents (e.g., corticosteroids, cyclosporine, methotrexate, adalimumab etc.) to control urticaria symptoms and they aim to prevent degranulation by preventing antibody formation.

The use of immunosuppressive agents is limited by their side-effect profile(s) and/or by their expensive cost (12). Our study showed a female predominance, similar to previous reports (13). In our study, age was comparable in both cases and control groups as ranged from 18 to 44 years in cases group with mean of

32.6 years and from 14 to 42 years in the control group with mean of 32.6 years. These results are also consistent with **Debberman et al. (2014)** regarding age as the mean of age in cases group was 39.5 years and in control group was 38.2 years with no significant statistical difference between both groups [(13)]. Our study showed that mean UAS-7 was nearly approximate in both groups at baseline, but there was significant decrease in mean UAS-7 in cases group as compared to control group at 4th week , 9th week of treatment and 12th week of follow. These results is consistent with a study done by Debbarman et al. (13) as they found that UAS-7 was comparable at baseline, and then decreased in both groups.

However; the comparison between both groups revealed significant decrease in UAS-7 in the AST group from 4 th week and till the end of six months of follow up. This study is consistent also with Patil et al. (14) who found that UAS-7 comes down within a few weeks. This study is consistent with the study done by Bajaj et al., (8) who founded that almost 60% of ASST (+) patients show a significant improvement in their signs and symptoms after nine weekly ASTs are given. This study is also consistent also with a study done in Egypt by Abdallah et al., (15) which concluded that both AWB and AST are effective in controlling urticarial symptoms in a significant number of ASST-positive patients.

They found that in in AST group, 60% were cured or had mild urticarial symptoms in 12th week. Kocaturk et al. (16) did not agree that this treatment method might represent a means of inducing specific tolerizing immune responses similar to those seen in specific immunotherapy; because the effect of treatment was more obvious during the injection period than after the injections were discontinued.

However, our study might have disagreed because Kocaturk et al included both ASST + and ASST - cases.

Finally, AST proved itself as an excellent adjuvant therapy because it reduced the urtcarial symptoms. AST was well-tolerated and only a few patients reported minor side effects as rash, itching and dizziness just after the first injection in 6 cases (25%) and AST as immunotherapy may predispose to autoimmunity disorders later on.

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