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Original Article

Dermatology Section

Autologous Whole Blood Therapy in Chronic Spontaneous Urticaria: A Comparative Study Between Autologous Serum Skin Test Positive and Negative Patients

MANJUNATH V MARIGERI[1], RADHAKRISHNAN SUBRAMANIYAN[2], MANASA SHETTISARA JANNEY[3], NAVYA DONAPARTHI[4]

ABSTRACT

Introduction: Chronic Spontaneous Urticaria (CSU) is frequently encountered in our day to day practice. Patients are often reluctant to take medicines for prolonged durations and seek interventions for rapid and prolonged remission. Autologous Whole Blood Therapy (AWBT) has been used with varied results in CSU and Autologous Serum Skin Test (ASST) reactivity has shown to influence the therapeutic response in some studies.

Aim: To compare the efficacy of AWBT in ASST positive versus negative CSU.

Materials and Methods: The present prospective, interventional, parallel group study was conducted in the Department of Dermatology, Command Hospital Air Force (tertiary care centre), Bangalore, India, from January 2014 to December 2015. Eight weekly injections of AWB (5 mL) were administered to 30 ASST positive and 30 age and sex matched ASST negative patients of CSU and followed-up for four weeks. Modified Urticaria Severity Score (MUSS) was recorded at baseline, 4th, 8th and 12th weeks to assess objective response to AWBT. Subjective response was documented as poor, satisfactory, good and excellent based on patient's feedback at the end of 12 weeks. Independent two-sample t-test, Chi-square (χ^2) test and cross tabulations were used to analyse the data through Statistical Package for the Social Sciences (SPSS) software version 21.0. A p-value of <0.05 was considered statistically significant.

Results: A total of 102 consenting patients were subjected to ASST, out of which 38 patients were ASST positive. After excluding those who were lost to follow-up, data from 30 ASST positive patients and corresponding age and sex matched ASST negative controls were analysed. Baseline MUSS of ASST positive group was significantly higher, indicating more severe nature of CSU. With AWBT, improvement in MUSS of ASST positive group (68.49±10.32%) was significantly higher than the ASST negative group (p-value <0.001) and ASST positive group required significantly lesser doses of rescue antihistamines (p-value <0.001) at the end of 12 weeks. Subjective response to AWBT was either good or excellent in both groups.

Conclusion: Although AWBT resulted in significant reduction of MUSS in ASST positive patients, it benefited patients in both groups irrespective of their ASST reactivity status. AWBT can be used as an effective adjuvant in the treatment of CSU.

Keywords: Antihistamines, Erythema, Modified urticaria severity score, Pruritus

INTRODUCTION

Urticaria is characterised by itchy transient erythematous oedematous eruptions of skin. It can be classified into acute (<6 weeks) or chronic (>6 weeks) based on duration of symptoms. In most cases of Chronic Urticaria (CU), despite exhaustive history taking, bedside tests and investigations, it is difficult to identify an inducer and these patients are classified as Chronic Spontaneous Urticaria (CSU) [1]. Autoimmune mechanisms and dysregulation of intracellular pathways predisposing to pathologic activation of mast cells and basophils are thought to play a major role in the pathogenesis of CSU [2].

Autologous Serum Skin Test (ASST), initially used by Sabroe RA et al., and modified later by many others, is a simple, rapid, in-vivo test used to identify patients with increased potential to develop urticaria due to endogenous circulating factors where facilities for sophisticated assays are not available [3]. Also, positive ASST correlates to higher urticaria activity score, higher levels of total serum immunoglobulin E, association with thyroid autoantibodies and angioedema [4].

Autologous Whole Blood Therapy (AWBT) or autohaemotherapy, was popularly used earlier in the treatment of several conditions like atopic dermatitis, urticaria, eczema, common cold, and orthopaedic diseases. It was discontinued in-between as being unscientific [5-7]. However, with increasing studies on ASST and discovery of role of circulating factors in CU, there has been a renewed interest in AWBT among dermatologists [4,8-12]. AWBT is postulated to work by inducing tolerance to Immunoglobulin (IgE), a high-affinity IgE receptor, also known Fc epsilon RI (FcεRI) and autoantigens. Also, it is thought to stimulate production of anti-idiotype antibodies against autoreactive IgE, which could block their binding to the FcεRI of mast cells or basophils. With autohaemotherapy, muscular dendritic cells process and present antigens to the immune system, with different immune response priming potential that may convert a previously disease causing antigen into a regulatory antigen that activates regulatory T cells [13].

Although AWBT is an old technique, it is not practiced by many. The objective of this study was to analyse the efficacy of AWBT in ASST positive and ASST negative CU patients and to encourage practitioners to revive this therapy.

MATERIALS AND METHODS

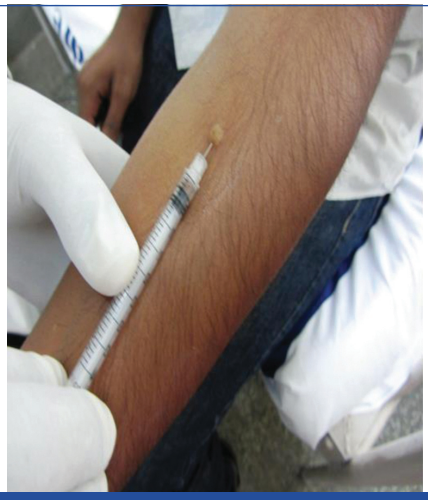
This was a prospective, interventional, parallel group study conducted in the Department of Dermatology, Command Hospital Air Force (tertiary care centre), Bangalore, India, from January 2014 to December 2015. Study was carried out after obtaining clearance from Institutional Ethics Committee.

Inclusion criteria: All patients above 18 years of age with CU were screened for eligibility. They underwent a detailed history taking, general physical examination, systemic examination and dermatologic examination. Investigations were done to rule out systemic diseases wherever suspected and indicated, and whoever eligible were included in the study.

Exclusion criteria: Patients with inducible urticaria, urticarial vasculitis, bronchial asthma, atopic dermatitis, collagen vascular diseases, immunosuppression and pregnant/lactating women were excluded from the study.

Study Procedure

After stopping all antihistamines for a minimum of three days, ASST was conducted by injecting 0.1 mL of patient's own serum and saline control intradermally into the flexor aspect of the forearm, 5 cm apart [Table/Fig-1]. A difference of >1.5 mm between the wheal diameters elicited by the autologous serum and saline, read after 30 minutes was considered positive ASST. Two equal age and sex matched groups of ASST positive and ASST negative patients were included in the study.



[Table/Fig-1]: ASST test being performed in a study subject.

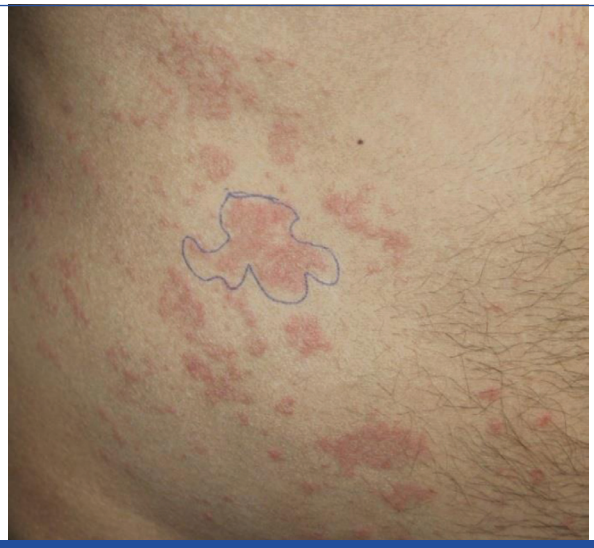
After obtaining informed consent, both groups received eight weekly doses of AWBT. The first dose was 2.5 mL and subsequent doses were 5 ml of venous blood, which was drawn from any accessible vein under aseptic precautions. The blood was re-injected immediately by deep intramuscular injection into alternate gluteal regions every week. Patients were observed for 30 minutes to look for immediate adverse effects after administration of AWBT. Patients were advised to take antihistamines (tablet fexofenadine 180 mg) only if they developed significant angioedema or breakthrough urticaria. After eight weekly doses of AWBT, patients in both the groups were on follow-up for four weeks.

Scoring system by Irinyi B et al., was adapted with few modifications by authors under the term MUSS and was used for objective assessment of improvement in this study [Table/Fig-2] [14]. It is based on a simple questionnaire encompassing details about number, size and duration of wheals, intensity and duration of pruritus, and duration of erythema [Table/Fig-3]. It was recorded at baseline, 4th week, 8th week and 12th week of the study. Based on this score, patients were classified into mild, moderate and severe urticaria. A score of 0-6 was classified as mild, 7-12 as moderate and 13-18 as severe. Percentage improvement in MUSS was assessed at every visit and documented as either poor (<25% improvement), satisfactory (26-50% improvement), good (51-75% improvement), or excellent (>76% improvement).

Subjective response was recorded as excellent, good, satisfactory or poor by patients at the end of 12 weeks. Other parameters such as need for rescue antihistamines to control the symptoms and adverse effects were also noted.

Parameters	Score value			
	0	1	2	3
Wheal number	Nil	<10	10-50	>50
Wheal size (cm)	Nil	<1	1-3	>3
Wheal duration (hour)	Nil	<1	1-24	>24
Pruritus intensity	Nil	Mild	Mod	Severe
Pruritus duration (hour)	Nil	<1	1-24	>24
Erythema duration (hour)	Nil	<1	1-24	>24

[Table/Fig-2]: Modified Urticaria Severity Score (MUSS) used in the study (modification of scoring system by Irinyi B et al.,) [14].



[Table/Fig-3]: Marking of margins to assess the size of wheals.

STATISTICAL ANALYSIS

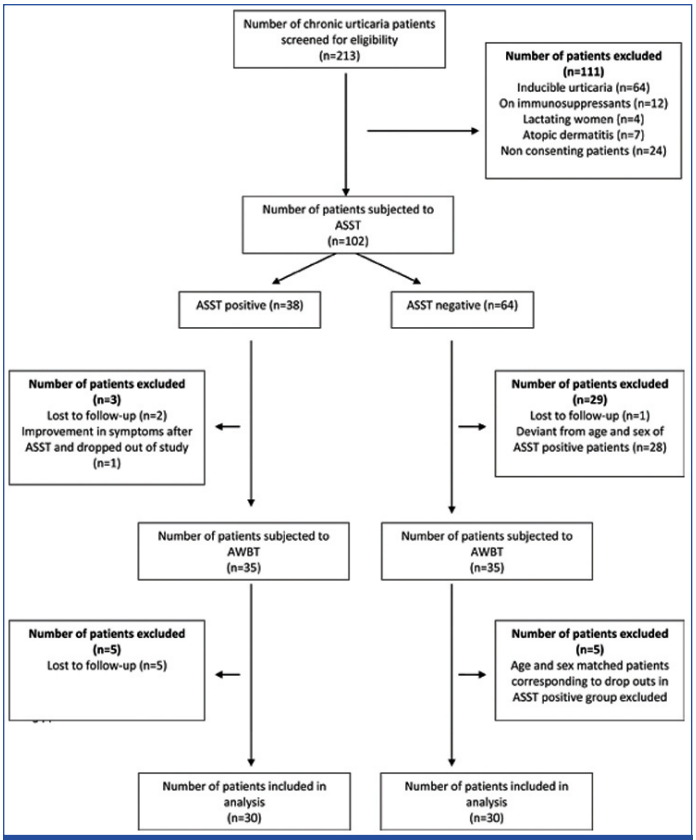
Statistical analysis of the data was conducted using Statistical Package for the Social Sciences (SPSS) software version 21.0 and tables and graphs were generated using Microsoft Excel software. Descriptive analysis was conducted to present the data in frequencies and percentages. Inferential analysis was conducted using independent two-sample t-test and p-value<0.05 was considered statistically significant. Cross tabulations were used to investigate the association between two or more categorical variables. The combined frequency distribution was evaluated using the Chi-square (χ^2) test.

RESULTS

Two hundred and thirteen patients were screened for eligibility in this study. After excluding unsuitable patients, ASST was performed in 102 patients. Thirty five successive ASST positive patients were recruited into the study. Among ASST negative patients, after excluding those not matching age and sex of ASST positive group, 35 ASST negative patients were included in the study. Some patients discontinued treatment due to transfers and some were excluded as they did not report for follow-up as shown in [Table/Fig-4]. Therefore, data of 30 patients from each group were considered for final statistical analysis.

Among 60 patients, 36 were males and 24 were females. Mean age of patients in this study was 33.48 years. The duration of diseases amongst ASST positive and negative groups were significantly different (Chi-square test, p-value <0.01). ASST positive CSU patients had significantly longer duration of disease when compared to ASST negative group. ASST positive group was also associated with higher Anti-thyroid Peroxidase (anti-TPO) antibody compared to ASST negative cases (t-test, p-value=0.032) [Table/Fig-5].

At baseline, the MUSS of ASST positive group was significantly higher (Chi-square test, p-value <0.0001) indicating more severe nature of illness when compared to ASST negative group [Table/Fig-6]. On initiating AWBT, a downward trend in MUSS was



[Table/Fig-4]: Flow diagram depicting sample selection and study design.

Parameters	ASST negative group	ASST positive group	p-value
Mean duration of disease	7.7 months	29.13 months	7.32e-17 **(<0.01)**
Abnormal anti-TPO levels	1 patient	7 patients	**0.032**

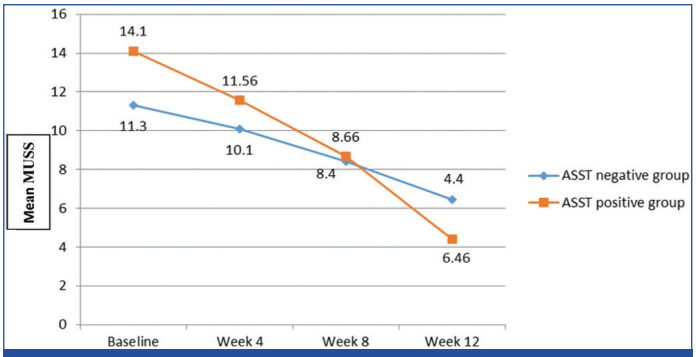
[Table/Fig-5]: Mean duration of disease, anti-TPO antibodies in ASST positive and negative groups.
p-value in bold font indicates statistically significant value

Week	Severity	ASST negative		ASST positive		χ^2	p-value
		Number of patients	%	Number of patients	%		
0	Mild	0	0.0	0	0.0	26.786	**<0.0001**
	Moderate	26	86.7	6	20.0		
	Severe	4	13.3	24	80.0		
4	Mild	0	0.0	0	0.0	1.176	0.236
	Moderate	27	90.0	24	80.0		
	Severe	3	10.0	6	20.0		
8	Mild	2	6.7	5	16.7	1.456	0.212
	Moderate	28	93.3	25	83.3		
	Severe	0	0	0	0.0		
12	Mild	21	70.0	29	96.7	7.68	**0.006**
	Moderate	9	30.0	1	3.3		
	Severe	0	0.0	0	0.0		

[Table/Fig-6]: Severity of urticaria based on MUSS during the course of the study in ASST positive and negative groups.

observed in both groups [Table/Fig-7,8]. Objective assessment of response to AWBT was carried out by analysing percentage improvement in MUSS at every visit. In ASST positive group, percentage improvement in MUSS was 68.49±10.32% and was significantly higher than the ASST negative group at 43.18±13.8% (Z-test, p-value <0.001) at the end of 12 weeks.

Majority of patients from both the groups reported either good or excellent improvement at the end of 12 weeks. One patient from ASST negative group reported poor improvement [Table/Fig-9]. There was a statistically significant difference in subjective response



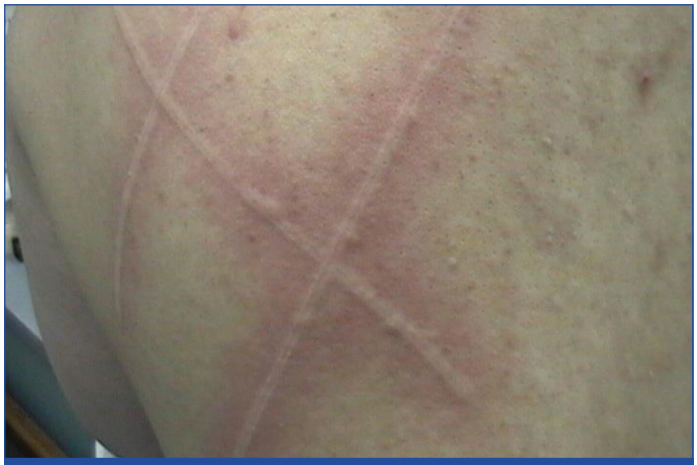
[Table/Fig-7]: MUSS of ASST positive and negative groups showing decreasing trend with monthly AWBT.

Mean MUSS	ASST positive group	ASST negative group
At 0 week	14.1	11.3
At 12 weeks	4.4	6.5

[Table/Fig-8]: Mean MUSS at baseline and at the end of 12 weeks in ASST positive and negative groups.

between the two groups at 12th week (Chi-square test, p-value <0.001) [Table/Fig-10].

During the course of this study, there was progressively lesser requirement of rescue antihistamines amongst ASST positive group compared to ASST negative group (Chi-square test, p-value <0.001 at 12th week). At baseline and at 4th week, ASST positive group required higher dose of antihistamines. At 12th week, ASST positive group required lesser doses of antihistamines than ASST negative group [Table/Fig-11]. Thus, authors can infer that ASST positive CSU responded better to AWBT than ASST negative CSU.



[Table/Fig-9]: Dermatographism in a patient with poor response to AWBT.

Subjective assessment		ASST negative group		ASST positive group		p-value
		Number of patients	%	Number of patients	%	
At 12 weeks	Poor	1	3.3	0	0	**0.001**
	Satisfactory	6	20	0	0	
	Good	20	66.7	7	23.3	
	Excellent	3	10	23	76.7	

[Table/Fig-10]: Subjective response to AWBT in ASST positive and negative groups as reported by patients at the end of follow-up period.

Antihistamines		ASST negative		ASST positive		χ2	p-value
		Number of patients	%	Number of patients	%		
Week 0	0/SOS	0	0	0	0	22.626	**<0.0001**
	1 tab	15	50	1	3.3		
	2 tab	14	46.7	12	40		
	3 tab	1	3.3	17	56.7		

Week 4	0/SOS	0	0	0	0		
	1 tab	24	80	5	16.7	25.208	**<0.0001**
	2 tab	6	20	19	63.3		
	3 tab	0	0	6	20		
Week 8	0/SOS	0	0	0	0		
	1 tab	25	83.3	20	66.7	2.222	0.116
	2 tab	5	16.7	10	33.3		
	3 tab	0	0	0	0		
Week 12	Nil	0	0	10	33.3	15.600	**0.001**
	SOS	8	26.7	7	23.3		
	1 tab	17	56.7	13	43.3		
	2 tab	5	16.7	0	0		
	3 tab	0	0	0	0		

[Table/Fig-11]: Significantly reduced requirement of rescue antihistamines by ASST positive and negative groups at the end of 12 weeks (p-value <0.05).

Pain at the injection site and increase in symptoms were the two adverse reactions observed in this study. About 24 (40%) patients experienced injection site pain, which spontaneously subsided in few hours. A small subset of ASST positive patients (n=5, 16.7%) reported increase in symptoms after AWBT during first few sessions; this however did not occur in ASST negative patients. There was no difference in adverse effects between the ASST positive and negative groups.

DISCUSSION

Chronic spontaneous urticaria is a common distressing dermatosis encountered in dermatology outpatient clinic. In the hope of finding a cure, the distressed patient often shifts from one dermatologist to another. Despite dermatologist's best efforts, no cause can be found in most cases. Up to 50% of patients with CU have circulating histamine releasing autoantibodies [15]. Patients with positive ASST are reported to have severe, prolonged disease course, require higher dose of antihistamines to control their symptoms [8,9,16]. Steroids, cyclosporine, omalizumab are established treatment modalities for ASST positive CU [1]. They are however reserved for refractory cases due to their adverse effect profile and high cost. Based on the theory of desensitisation, AWBT can induce tolerance to circulating histamine releasing factors. But, a recent review could not ascertain the efficacy of AWBT in CU conclusively due to lack of sufficient studies [7]. This study was aimed at assessing the efficacy of AWBT in CSU and its differential response in ASST positive and negative subset of patients.

In this study, it was observed that ASST positive group had longer duration of illness with higher severity. This was similar to the observations by Staubach P et al., wherein ASST positive CSU patients reported longer duration of symptoms (109±31 months) than ASST negative patients (30±9 months) [10]. In another study by Bajaj AK et al., duration of urticaria in ASST positive patients ranged from 6 months to 32 years and in ASST negative patients it ranged from 6 months to 10 years. Also, in their study, ASST positive group had severe urticaria (Urticaria score-24/30) when compared to ASST negative group, similar to the present study findings [11]. Vohra S et al., also reported higher mean urticaria activity score (>5 in 96% of ASST positive patients), frequent involvement of more body sites, particularly palms and soles, presence of throat angioedema and general constitutional, respiratory or gastrointestinal symptoms in ASST positive group [12].

Autoimmune thyroid diseases with IgG antibodies against thyroid peroxidise, thyroglobulin, Thyroid Stimulating Hormone (TSH) receptor, antithyroid microsomal antibodies, IgE anti-TPO antibodies are documented to be significantly associated with an increased risk of CSU [17-19]. Hence, anti-TPO levels were tested in this study and there was a significant association with ASST positivity.

Autologous whole blood therapy has been controversial since its description. Although some studies have denied any difference in response between ASST positive and negative patients, they have not dismissed the beneficial effects of AWBT [20-22]. Authors observed a steady decline in MUSS on repeated injections of AWB in both groups accompanied by reduced need for rescue antihistamines and better patient satisfaction. However, the response was significantly better in ASST positive group similar to findings by Staubach P et al., [10]. There was 41% reduction in MUSS when compared to ASST negative group (21%) and placebo (18%). Also, ASST positive patients required less than half of the antihistaminic rescue medication they had taken before therapy. In another retrospective study by Tseng JT et al., 8/9 ASST positive patients responded to eight weekly AWB injections as compared to 2/8 ASST negative patients [23].

In addition to minor adverse effects (pain, soreness, bruising at injection site) noted by many authors, authors also found transient increase in wheal and pruritus in some of the study patients in initial four weeks. However, no events of anaphylaxis, serious infections or allergy were observed.

As observed in the present study, AWBT works in both ASST positive and negative patients. The variations in methodology, population under study, crude technique of ASST, false positive/negative results may make ASST unreliable at times. Therefore, ASST reactivity may not reliably reflect the chances of response to this form of therapy.

Limitation(s)

Authors could not include healthy volunteers and placebo group in the present study due to ethical concerns. Also, the small sample size is a limitation of this study. Larger studies are required to validate the results.

CONCLUSION(S)

One of the most challenging aspects in the management of the ASST positive CSU patients is its severity, recurrence, requirement of high dose of antihistamines and also the need for prolonged immunosuppression at times. AWBT is a promising, effective, economical and safe modality of treatment for ASST positive CSU and a very effective adjuvant in the treatment of ASST negative CSU. AWBT is worth trying in CU cases before considering immunosuppressants and biologicals.

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PARTICULARS OF CONTRIBUTORS:
1. Specialist Medical Officer, Department of Dermatology, Haveri Institute of Medical Sciences, Haveri, Karnataka, India.
2. Professor, Department of Dermatology, Army College of Medical Sciences, Delhi, India.
3. Assistant Professor, Department of Dermatology, Command Hospital Air Force, Bangalore, Karnataka, India.
4. Associate Professor, Department of Dermatology, Command Hospital Air Force, Bangalore, Karnataka, India

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Navya Donaparthi,
Associate Professor, Department of Dermatology, Command Hospital Air Force, Bangalore, Karnataka, India.
E-mail: navya.donaparthi@gmail.com

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