

EFFECTIVENESS OF AUTOLOGOUS SERUM THERAPY IN CHRONIC URTICARIA: A PROSPECTIVE OBSERVATIONAL STUDY IN TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

Chronic urticaria is a challenging condition, both for patient and physician in a day-to-day practice. There is constant search for newer modality of treatment, which can provide prolong remission with less side effect. Autologous serum therapy have shown promising result in initial studies.

AIM

To evaluate effectiveness of Autologous Serum Therapy in chronic urticaria patients.

MATERIALS AND METHODS

A prospective observational study. Total 220 patients enrolled for study. Autologous serum skin test performed in all patients; 113 patients were given Autologous Serum Therapy along with oral levocetirizine on SOS basis weekly and 107 patients were given only oral levocetirizine on demand basis. Response to treatment assessed by urticaria activity score, urticaria total severity score, antihistamine score, dermatological quality of life index and Likert scale on 2 weekly interval for 10 weeks.

RESULTS

Autologous Serum Therapy shown significant improvement in both Autologous Serum Skin Test positive and Autologous Serum Skin Test negative patients as compared to non-Autologous Serum Therapy groups. Autologous Serum Therapy is more effective in Autologous Serum Skin Test positive patients.

CONCLUSION

Autologous Serum Therapy is effective in chronic urticaria patients.

KEYWORDS

Autologous Serum Therapy Chronic Urticaria, Autologous Serum Skin Test.

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INTRODUCTION

Urticaria is defined as a skin lesion consisting of a wheal-and-flare reaction in which localized intracutaneous oedema (Wheal) is surrounded by an area of redness (Erythema) that is typically pruritic.¹ Urticaria persisting beyond 6 weeks are considered chronic.¹ Antihistamines are the mainstay of management.²

Autologous Serum Therapy^{3,4,5,6,7}

It is comparatively newer modality of therapy, in which patients own blood is withdrawn and serum is prepared via centrifugation and injected intramuscularly. Initial study has shown that it improves urticaria symptoms, reduces doses of antihistamines and improves quality of life of patients. Basis of this treatment is Autologous serum containing tolerance-generating anti-idiotypic antibodies to mast cell degranulating antigens.

MATERIAL AND METHOD

The study was conducted in tertiary care institute in eastern UP. Institutional ethical committee permission obtained prior to commencement of study. Study design was prospective observational study. Patients were allotted in two groups by systemic random sampling. Informed written consent was taken from all study participants. Chronic urticaria was

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diagnosed clinically as wheal-and-flare reaction, in which localized intracutaneous oedema (Wheal) is surrounded by an area of redness (Erythema) that is typically pruritic. Urticaria persisting beyond 6 weeks are considered chronic. Inclusion criteria includes patient having almost daily appearance of wheals for ≥6 months, patient willing to take part in study and signed written informed consent, patient willing to come for weekly followup for 10 weeks, Age between 18 years to 60 years and free from any infective or immunosuppressive condition. Exclusion criteria were pregnant and lactating women, patient on steroid or other immunosuppressive, patient suffering from any infective condition, addicted to substance abuse. First group was given Autologous Serum Therapy along with oral levocetirizine 5mg on demand basis and second group was only on oral levocetirizine 5mg on demand basis.

Baseline investigation performed including complete blood count, liver function test, kidney function test, HIV, HBsAg, serum electrolyte, serum Thyroid Stimulating Hormone level.

Material required for study

1. Centrifuge machine.
2. Syringe and needle.
3. Vacutainers.
4. Insulin Syringe.
5. Gloves.
6. Normal Saline.
7. Scale.



Autologous serum skin test.⁸ was performed by withdrawing 5mL blood in disposable syringe under aseptic

precaution. Blood is then transferred to disposable vacutainers and centrifuged at 2000rpm for 10 minutes; then upper clear portion which is serum was separated in insulin syringe; 0.02mL serum injected in one forearm and normal saline injected in other forearm as control. If test arm erythema was more than 1.5mm in perpendicular diameter than that of control then it is considered as Autologous Serum Skin Test positive and less than 1.5mm is considered as Autologous Serum Skin Test negative.



Autologous Serum Skin Test given



Autologous Serum Skin Test Negative



Autologous Serum Skin Test given



Autologous Serum Skin Test Positive

Autologous serum therapy was performed by withdrawing 5mL blood in disposable syringe under aseptic precaution. Blood is then transferred to disposable vacutainers and centrifuged at 2000rpm for 10 minutes; 2mL serum separated with help of disposable syringe, then injected intramuscularly at buttock. Treatment repeated every week.

Assessment Parameters.^{9,10}

- Urticaria activity score.
- Urticaria total severity score.
- Antihistamine score.
- Likert scale.
- Dermatological quality of Life Index.

Urticaria Activity Score

Wheal

Score

- 0 -none
- 1 - Mild (20 wheal/24-hour)
- 2 - Moderate (20-50 wheals/24-hour)
- 3 - Intense (>50 wheals/24-hour)

Pruritus

Score

- 0 -none
 - 1 - Mild (present but not annoying/troublesome)
 - 2 - Troublesome but does not interfere with sleep
 - 3 - Severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep
- Weekly urticaria activity score is calculated by adding daily UAS for 1 week, so score ranges from 0-42.

Urticaria Total Severity Score

1. Number and size of wheals,
 2. Intensity of pruritus,
 3. Duration of persistence of lesions,
 4. Frequency of appearance of lesions,
 5. Frequency of antihistamine use,
- With each parameter having a score of 0-3, maximum score being 18.
- 5-point Likert scale
 0: No improvement,
 1: Mild improvement,
 2: Moderate improvement,
 3: Marked improvement,

4: Excellent improvement.

Antihistamine score

- 0 - no pill/week
- 1 - once/week
- 2 - 2-3 times/week
- 3 - daily

DERMATOLOGY LIFE QUALITY INDEX

Consists of series of questionnaires related to daily routine of life. Each parameter is scored as very much, a lot, a little, not at all and not relevant and score as 3, 2, 1 and 0. Total score ranges from 0-30. Each parameter was documented at 0, 2, 4, 6, 8 and 10th week.

Statistical Analysis

Statistical test - t test and null hypothesis

RESULTS

	Autologous Serum Skin Test Positive	Autologous Serum Skin Test Negative	Total
Group 1	74 (65.48%)	39 (34.52%)	113 (100%)
Group 2	69 (64.49%)	38 (35.51%)	107 (100%)
Total	143 (65%)	77 (35%)	220 (100%)

Table 1: Autologous Serum Skin Test Results

In this study in Group 1, out of 113 patients (100%) 74 patients (65.48%) were Autologous Serum Skin Test positive and 39 patients (34.52%) were Autologous Serum Skin Test negative. In Group 2, out of 107 patients (100%), 69 patients (64.49%) were Autologous Serum Skin Test positive and 38 patients (35.52%) were Autologous Serum Skin Test negative. Overall, 65% patients were Autologous Serum Skin Test positive.

	Male	Female	Total
Group 1	41 (36.28%)	72 (63.72%)	113 (100%)
Group 2	38 (35.51%)	69 (64.49%)	107 (100%)
Total	79 (35.91%)	141 (64.09%)	220 (100%)

Table 2: Distribution of Subjects According to Sex

Out of 220 patients, 79 patients were male and rest 141 patients were female. On percentage basis, 35.51% were male and rest 64.09% were female. In group 141 patients (36.28%) were male and 72 patients (63.72%) were female. In Group 2, 38 patients (35.91%) were male and 69 patients (64.49%) were female.

Sl. No.	Age Group	Female	%	Male	%	Total (%)
1	18-20 year	18	12.58 %	10	12.98%	28 (12.73%)
2	20-30 year	45	31.47 %	24	31.17%	69 (31.36%)
3	30-40 year	38	26.95 %	23	29.11%	61 (27.73 %)
4	40-50 year	18	12.59 %	14	18.18%	32 (14.55%)
5	50-60 year	22	15.38 %	8	10.39%	30 (13.64%)
Total		141	100 %	79	100%	220 (100%)

Table 3: Distribution of Study Subjects According to Age

Out of 220 patients, 18 (12.58%) female and 10 male (12.98%) belong to age group 18 to 20 years; 45 (31.47%)

female and 24 male (31.17%) belong to age group 20 to 30 years; 38 (26.95%) female and 23 male (29.11%) belong to age group 30 to 40 years; 18 (12.59%) female and 14 male (18.18%) belong to age group 40 to 50 years; 22 (15.38%) female and 8 male (10.39%) belong to age group 50 to 60 years. Most patient belong to 20 -30 years (31.36%) and 30-40 years age group (27.73%).

Out of total 220 patients, 89 patients (40.45%) belong to rural area and 131 patients (59.55%) belong to urban population. In Group 1, 36 (16.36%) patients were from rural background and 43 (19.55%) were from urban background. In Group 2, 53 (24.09%) patients were from rural area and 88 (40%) were from urban area.

Sl. No.	Rural	Urban	Total
Male	36 (16.36%)	43 (19.55%)	79 (35.91%)
Female	53 (24.09%)	88 (40 %)	141 (64.09%)
Total	89 (40.45%)	131 (59.55%)	220 (100%)

Table 4: Distribution of Study Subjects According to Residence

Sl. No.	Parameter	(n=74) Mean (Starting of Therapy)	(n=74) SD	(n=74) Mean (End of Therapy)	(n=74) SD	t-value	P value	Significance
1	UAS	28.00	3.29	26.11	3.96	3.159	0.0019	Significant
2	UTSS	14.39	1.57	12.64	1.19	7.68	0.0001	Significant
3	Antihistamine score	3	0	2.38	0.62	8.62	0.0001	Significant
4	DQLI	19.69	2.11	17.93	2.92	4.1969	0.0001	Significant

Table 5: Statistical Analysis for Autologous Serum Skin Test Positive Patients in Group 1

In Autologous serum skin test positive patients of Group 1, null hypothesis and unpaired 't' test applied for urticaria activity score, urticaria total severity score, antihistamine score and dermatological quality of life index. Test shown significant improvement (p value <0.05) in all parameters after treatment.

Sl. No.	Parameter	(n=39) Mean (Starting of Therapy)	(n=39) SD	(n=39) Mean (End of Therapy)	(n=39) SD	t-value	P value	Significance
1	UAS	28.13	3.31	26.31	3.86	3.159	0.0019	Significant
2	UTSS	14.82	1.70	13.56	3.21	2.16	0.0339	Significant
3	Antihistamine score	3	0	2.55	0.096	4.71	0.0001	Significant
4	DQLI	19.38	1.99	18.03	2.83	2.45	0.0166	Significant

Table 6: Statistical Analysis for Autologous Serum Skin Test Negative Patients in Group 1

In Autologous serum skin test negative patients of Group 1, null hypothesis and unpaired 't' test applied for urticaria activity score, urticaria total severity score, antihistamine score and dermatological quality of life index. Test shown significant improvement (p value <0.05) in all parameters after treatment.

Sl. No.	Parameter	(n=69) Mean (Starting of Therapy)	(n=69) SD	(n=69) Mean (End of Therapy)	(n=69) SD	t-value	P value	Significance
1	UAS	29.50	3.21	28.13	3.70	1.7220	0.0892	Not Significant
2	UTSS	14.82	1.70	13.56	3.21	2.16	0.0339	Not Significant
3	Antihistamine score	3	0	2.96	0.0810	1.76	0.083	Not Significant
4	DQLI	21.14	1.96	20.48	2.36	1.81	0.0732	Not Significant

Table 7: Statistical Analysis for Autologous Serum Skin Test Positive Patients in Group 2

In Autologous serum skin test positive patients of Group 2, null hypothesis and unpaired 't' test applied for urticaria activity score, urticaria total severity score, antihistamine score and dermatological quality of life index. Test does not show significant improvement (p value >0.05) in all parameters after treatment.

Sl. No.	Parameter	(n=38) Mean (Starting of Therapy)	(n=38) SD	(n=38) Mean (End of Therapy)	(n=38) SD	t-value	P value	Significance
1	UAS	29.50	3.21	28.13	3.70	1.7220	0.0892	Not Significant
2	UTSS	14.24	1.34	13.76	1.55	1.42	0.1589	Not Significant
3	Antihistamine score	3	0	2.95	0.23	1.43	0.156	Not Significant
4	DQLI	21.13	2.09	20.32	2.26	1.6338	0.1086	Not Significant

Table 8: Statistical Analysis for Autologous Serum Skin Test Negative Patients in Group 2

In Autologous serum skin test negative patients of Group 2, null hypothesis and unpaired 't' test applied for urticaria activity score, urticaria total severity score, antihistamine score and dermatological quality of life index. Test does not show significant improvement (p value >0.05) in all parameters after treatment.

	Group 1		Group 2	
	Autologous Serum Skin Test Positive	Autologous Serum Skin Test Negative	Autologous Serum Skin Test Positive	Autologous Serum Skin Test Negative
No improvement	20 (27.02%)	14 (35.89%)	34 (49.28%)	18 (47.37%)
Mild improvement	23 (31.08%)	12 (30.77%)	29 (42.03%)	17 (44.74%)
Moderate improvement	19 (25.68%)	8 (20.51%)	6 (8.70%)	3 (7.90%)
Marked improvement	8 (10.81%)	4 (10.26%)	0 (0%)	0 (0%)
Excellent improvement	4 (5.41%)	1 (2.56%)	0 (0%)	0 (0%)
Total	74 (100%)	39 (100%)	69 (100%)	38 (100%)

Table 9: Likert Scale

In Group 1 out of 74 Autologous serum skin test positive patients, 20 patients (27.02%) shown no improvement, 23 patients (31.08%) shown mild improvement, 19 patients (25.68%) shown moderate improvement, 8 patients (10.81%) shown marked improvement and 4 patients (5.41%) shown excellent improvement.

In Group 1 out of 39 Autologous serum skin test negative patients, 14 patients (35.89%) shown no improvement, 12 patients (30.77%) shown mild improvement, 8 patients (20.51%) shown moderate improvement, 4 patients (10.26%) shown marked improvement and 1 patient (2.56%) shown excellent improvement.

In Group 2, out of 69 Autologous serum skin test positive patients, 34 patients (49.28%) shown no improvement, 29 patients (42.03%) shown mild improvement, 6 patients (8.70%) shown moderate improvement, no patient shown marked or excellent improvement.

In Group 2, out of 38 Autologous serum skin test negative patients, 18 patients (47.37%) shown no improvement, 17 patients (44.74%) shown mild improvement, 3 patients (7.90%) shown moderate improvement, no patient shown marked or excellent improvement.

DISCUSSION

Urticaria is characterized by transient skin or mucosal swellings due to plasma leakage. Wheals are characteristically pruritic and pink or pale in the center.¹

All urticarias are acute initially. Some will become chronic after a period of time that is usually defined as 6 weeks or more.²

Estimates of the lifetime occurrence of urticaria range from less than 1% to as high as 30% in the general population, depending on the age range and method of sampling. The true figure is likely to be in the range of 1–5%.¹

Overall, urticaria is more common in women with a female:male ratio of approximately 2:1 for chronic urticaria, but the ratio varies with the different physical urticarias.¹

The mast cell is the primary effector cell of urticaria. Cross-linking of two or more adjacent FcεRI on the mast cell membrane will initiate a chain of calcium- and energy-dependent steps leading to fusion of storage granules with the cell membrane and externalization of their contents. This is known as degranulation.¹¹

Classic immediate hypersensitivity reactions involve binding of receptor-bound specific IgE by allergen. There are several recognized immunologic degranulating stimuli that act through the IgE receptor, such as anti-IgE and anti-FcεRI antibodies.¹² Other non-immunologic stimuli including opiates, C5a anaphylatoxin, stem cell factor and some neuropeptides (e.g. substance P) can cause mast cell degranulation by binding specific receptors, independent of the FcεRI. Mast cell granules contain preformed mediators of inflammation, the most important of which is histamine.¹³

Histamine and other proinflammatory mediators released on degranulation bind receptors on post-capillary venules in the skin leading to vasodilatation and increased permeability to large plasma proteins including albumin and immunoglobulins. Furthermore, histamine, TNF-α and IL-8 upregulate the expression of adhesion molecules on endothelial cells, thereby promoting the migration of

circulating inflammatory cells from the blood into the urticarial lesion.¹³

Functional IgG autoantibodies that release histamine (And other mediators) from mast cells and basophils have been detected in the serum of 30-50% of patients with chronic 'ordinary' urticaria using in vitro assays.¹¹ Sera of approximately 60% of patients with chronic ordinary urticaria have been shown to cause a pink wheal when injected intradermally into the patient's own skin (The autologous serum skin test).⁸ In our study, 65% patients shown positive Autologous serum skin test. Antihistamines are the mainstay of management. This is first line treatment for urticaria.² The use of serum in place of whole blood is the modification that has been used by Bajaj, et al.³

Whole blood therapy had been tried in many autoimmune diseases including pemphigus, severe dry eye (Due to Sjogren's syndrome, rheumatoid arthritis, etc.) and diseases like viral illness like herpes, cancer, allergic diseases like atopic dermatitis.^{14,15,16,17} Potential of whole blood in the treatment of urticaria was documented by Fleck M.¹⁸ and Staubach et al.¹⁴ in separate studies and later use of serum in the treatment of urticaria was highlighted by Bajaj, et al.³ The plausible mechanism of action of autologous serum therapy was thought to be induction of anti-idiotypes, which have recently been shown to inhibit the function of disease-inducing antibodies in pemphigus and also to shift the Th2 cytokine profile to Th1 in Autologous serum skin test + patients.¹⁴

Different studies had been conducted on autologous serum therapy. Staubach, et al.¹⁴ reported improvement in 70% Autologous serum skin test positive patients. Bajaj, et al.³ reported improvement in 60% Autologous serum skin test positive patients. Panchami Debbarman et al.⁷ also found Autologous serum therapy beneficial in chronic urticaria. Sharmila Patil, et al.⁶ gave autologous serum therapy to 20 patients excellent improvement was seen in 9 patients, 6 patients did not show satisfactory response and five patients showed no response. In our study, 41.9% Autologous serum skin test positive patient and 33.33% Autologous serum skin test negative patients shown moderate-to-excellent improvement.

CONCLUSION

Autologous serum therapy is proved effective in chronic urticaria patients, specially in Autologous serum skin test positive patients.

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