Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16118
DOI URL: http://dx.doi.org/10.21474/IJAR01/16118

RESEARCH ARTICLE

A COMPARATIVE STUDY OF SAFETY AND EFFICACY OF AUTOLOGOUS SERUM THERAPY (AST) IN (+VE) AND (-VE) CHRONIC SPONTANEOUS URTICARIA PATIENTS

Dr. Monisha Narayanappa, Dr. Sharath Kumar B.C and Dr. Jai Kumar Pillai
Department of Venereology and Leprosy, KIMS, Bengalore.

Manuscript Info

Manuscript History
Received: 30 November 2022
Final Accepted: 31 December 2022
Published: January 2023

Key words:-
Autologous Serum Therapy -AST, UAS-**U**rticaria Activity Score (UAS), DLQI, CSU

Abstract

The Chronic Spontaneous Urticaria (CSU) is a common and distressing skin condition that causes red , raised , itchy and sometimes painful hives or wheals (raised rash or patches) on the skin without known obvious trigger. It present daily for at least six weeks and is referred to as spontaneous when symptoms are not triggered by a known cause. The CSU is an unpredictable and debilating condition which can affects daily life in many ways, including sleep deprivation , anxiety and social isolation. Due to the lack of literature on CSU at the population level, proximal treatment algorithms are developed in limited resource countries. In this pragmatic approach, many studies have explored such treatment and challenges worldwide. The current study makes an effort to show the safety and effectiveness of autologous serum therapy in autologous serum therapy (+ve) and (-ve) groups in this setting. 200 (autologous serum therapy +ve and -ve) CSU known patients were administered autologous serum therapy in various time intervals (from the baseline to the eighth week). Each follow-up patient was closely observed, and any adverse events (safety and efficacy) were recorded. The Dermatologic Life Quality Index and the Urticaria Activity Score (UAS) were used to evaluate all patients (DLQI). According to the findings, there were substantial improvements in the UAS-7 and DLQI at the eight and twelfth weeks (P=0.001). Mild erythema and pain at the injection site were the only unfavourable reactions seen (9%) in participants overall, with strong specificity (98.11%), sensitivity (89.56%), PPV (75.42), NPV-(71.24), accuracy (80.52), and odds ratio (>1). In conclusion, many patients may benefit from this more recent medication, which has been proved to be more effective and safe.

Introduction:-

Chronic urticaria is a common and distressing dermatoses characterized by the appearance of evanescent wheals almost daily, continuously for six or more weeks [1] Patients experience restrictions in daily life activities and social life due to unrelenting symptoms, exhibits psychiatric co-morbidities, sexual difficulties and reduced life quality index . Chronic Spontaneous Urticaria Patients (CCU) requires long term treatment with medications having potentially hazardous side effects, without a definite treatment period and hence, patient compliance and satisfaction level was reduced. In its extremely severe form, can pose a therapeutic challenge to the treating physician and a

Corresponding Author:- Dr. Monisha Narayanappa
Address**:-** Department of Venereology and Leprosy, KIMS, Bengalore.

protracted, unsatisfactory ordeal for the patient. autologous serum therapy is a simple in-vivo intradermal clinical test for the detection of basophil histamine releasing activity and aids in identifying chronic autoimmune urticaria. autologous serum therapy has been found to have a sensitivity of approximately (70%) and a specificity (80%) .[4-6]AST shows promise in treatment of urticaria regardless of the autoreactive nature.[8] Auto-hemotherapy can induce tolerisation /desensitisation of ar-CU patients to the proinflammatory signals expressed in their circulation. There is no risk of rejection or disease transmission as it is produced from patients own blood in their circulation. Therapy could be useful in India as it is economical, cost effective and does not involve use of various expensive drugs like cyclosporine and omalizumab. Minimum instruments like centrifuge, syringe and needles are required for the procedure.[10] we attempted to compare the safety and efficacy of autologous serum therapy in autologous serum therapy +ve and –Ve CSU patients. This will give knowledge for dermatologists and patients, since this has a significant bearing on the long term management of these patients in terms of need to use supra pharmacologic doses of antihistamines or immunomodulators.

Methods:-

A prospective comparative parallel group interventional study with Chronic Spontaneous Urticaria Patients (CSU) patients satisfying the following inclusion and exclusion criteria. A total 100 subjects in each groups (autologous serum therapy +ve and –Ve) were included in this study .The following inclusion criteria and exclusion critera was employed for recruitment of patients viz (i) Chronic spontaneous urticaria (ii)Off antihistamines for 1 week (iii)Age >18yrs and < 70 years with history of chronic spontaneous urticaria (iv) Known patients .The exclusion criteria was (i)

Pregnant and lactating females (ii) Patients on long term systemic steroids or immuno-suppressants in the past six weeks (iii) Physical urticaria and Urticaria associated with other systemic diseases etc.

Patients Screening Visit

After study intervention, the patient's demographic details and history of disease was recorded and the severity of their urticaria was assessed based on (Urticaria Activity Score (UAS @ 7 weeks) . All patients were evaluated for any underlying cause by means of a proper clinical examinations and relevant investigations and those with no identifiable cause, were assessed for the presence of autoantibodies by performing autologous serum therapy . Run-in period of 7 days was given prior to the autologous serum therapy , when subjects were asked to discontinue any antihistamines they had been using.

Baseline visit

Autologous serum therapy was performed in all study subjects and the results were recorded after 30 min (as detailed below). The CSU patients were received autologous serum therapy, irrespective of the results on autologous serum therapy and patients were instructed to consume anti histamines on-demand basis (experiencing wealing or itching). Any subject experiencing intolerable symptoms of urticaria were instructed to contact the investigators.

Follow-up visit

AST was given for eight consecutive weeks and the patients were followed-up action was done for the improvement or recurrence of symptoms after four weeks of stopping AST. Prednisolone tablet (1mg/kg body weight) was kept as rescue medications. The cclinical assessment was done at baseline, @ $4^{th,}$ 8^{th} and 12^{th} weeks and efficacy, safety parameters were noted. The assessment tools are (i) Urticaria activity score (UAS) and (ii) Dermatology life quality index (DLQI)

Autologous Serum Skin Test

A two ml of patient's venous blood was drawn with a sterile disposable syringe from the antecubital vein in sterile Vacutainer for serum collection. Allow to clot for 20 mins. The blood was subjected to centrifugation at the rate of 2000 rpm for 15 min at room temperature. 0.05 ml of the serum thus separated, is injected immediately intra-dermal into the patients left flexor forearm two inches below the antecubital crease and 0.05 ml sterile normal saline as negative control into right forearm using 31G sterile disposable 1 ml insulin syringe. Areas involved in spontaneous wealing within last 48 hours are avoided. A reading of the wheal was taken after 30 min. autologous serum therapy was considered +ve when the average of two perpendicular diameters of autologous serum wheal is >1.5mm than the normal saline induced wheal.

Intervention- Autologous serum therapy (AST)

Two ml of the fresh serum separated from the patients' blood (as stated below) was given deep IM into the gluteus muscle for 9 successive weeks (baseline and initial 8 follow-up-visits). During the study intervention we collected 5cc of venous blood in a plain vacutainer. Allow to clot for 20 minutes, Centrifugation at 3000 rpm for 10 mins. Use 5cc syringe and separate serum. Inject 2 ml of the serum deep intramuscularly into the gluteus muscle using 22 no needle simultaneously we repeated the procedure for 8 consecutive weeks. Blood collection procedure was used to ensure identity of the donor is verified and the labelling was corrected to avoid injecting of wrong serum. Standard precautions were maintained for handling blood products to protect both the patient and the operator. Patients assessment was done by Urticaria activity score (UAS) and Dermatologic Life Quality Index (DLQI) are used as primary effectiveness variables. The scores were calculated for safety and efficacy at week 0(baseline), week 4, week 8(end of treatment) and week 12 beside with vital signs and spontaneously reported adverse events , assessed at every weeks follow-up. Clinical assessment was reduced by > 30% in both urticaria activity score (UAS) and scores of dermatology quality life index (DLQI) @ week 8 and weeks of 12 compared to baseline and also considered as improvement for both the groups.

Statistical Analysis

The collected data was analysed by using SAS. Multivariate linear regression, spearman ranks correlation co-efficient, paired and unpaired statistical method was employed to test the hypothesis. However, the changes or association of the variables were rejected ($p>0.01$) or accepted based on the probability value ($P\leq0.01$).

Results:-

A total of 200 patients were included in this study (n_1 =100 autologous serum therapy +ve) and (n_2= 100 autologous serum therapy -ve) with males (54%) and females (46%), sex ratio is 1:1. Majority of patients belonged to age group 36-45 years in both the autologous serum therapy +ve (51%) and –ve (34%). The mean onset of (+ ve) group was (29.17+/-2.14) years and (-ve) group was (30.62+/-5.18) years. Mean duration of symptoms in the (+ve) group was (3.48+/-1.62) years and (–ve) group was (2.73+/-3.73) years. Males were more predominant (54%). The history of atopy of males (13%) of total subjects and it was higher in (–ve) group. A Personal histories like non-vegetarian diet (76%), alcohol and smoking (>85%) is significantly increased incidence and also it was more common in (+ve) as compared (85%) with negative group ($p<0.01$) .There was declined trend was seen in UAS-7 for both groups at different time intervals , @ 4^{th} and 8^{th} weeks follow-up trend was declined and it was continued up to 12^{th} weeks. The improvement was slightly more in the (+ve) as compared with (-ve) group, though the differences were not found to be significant ($p>0.01$). The percentage of patients showed (>30%) improvements in the UAS-7 @ 8^{th} weeks as compared to baseline (65.52%) in (+ve) & (-ve) was (61.22%) ($p<0.01$) . The percentage expression at the end of the study (@12^{th} weeks among autologous serum therapy +ve was (70.16%) and –ve was (66.33%) groups it was found to be significant ($p<0.01$). An improvement in the DLQI was seen on 8^{th} - 12^{th} weeks follow up ($p>0.01$). Since (>30%) patients were showed improvements in the DLQI @ 8^{th} and 12^{th} weeks in +ve (69.81%) & -ve (73.62%), both the groups were expressed good improvement in UAS-7 and DLQI ($p<0.01$). At the follow up end meagerly (2%) +ve subjects has required with anti histamine. There is no serious adverse effects among the cases, only mild reactions (<1%) were noticed in the form of injection site pain and transient erythema (9%).

Table 1:- Comparison of Age distribution.

Age group (Years)	Autologous serum therapy		Hazard risk ratio	P-value
	(+ve) (n=100)	–Ve (n=100)		
16-25	23	31	1.22	≤0.001
26-35	51	34	2.69	≤0.001
36-45	18	26	1.85	≤0.001
46-55	8	7	1.66	≤0.001
56-65	0	2	-	-
Duration(Years)	3.482±1.62	2.739±3.73	2.33	0.023
Age of onset (Years)	29.17±2.14	30.62±5.18	4.33	≤0.001
Co morbidities				
Nothing significant	88	86		>0.001

History of atopic dermatitis	12	14		≤0.001

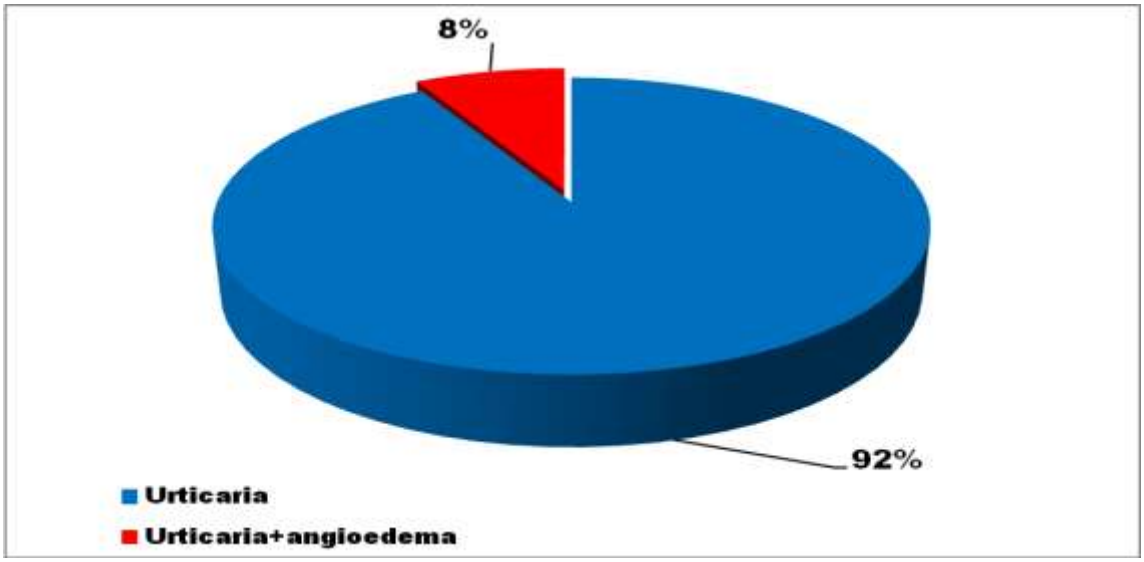


Fig 1:- Distribution of symptoms.

Efficacy parameters

The distribution of symptoms were correlated by past history (H/o) , the urticaria (8%) and urticaria associated with angioderma (92%) both symptoms significantly correlated with age (mean age) and irrespective of gender (Fig 1) . The response to AST in the +ve and –ve study subjects were assessed by UAS-7 and DLQI with different time intervals, the baseline, @ 4th, 8th and 12th weeks follow-up period was compared between each groups. Asper the results (>30%) improvement was seen in UAS-7 and DLQI @ 8th and 12th weeks.

Table 2:- Comparison of weekly urticaria activity score and weekly pruritus and wheals between the study groups at various follow-up weeks.

Follow-up week	UAS Parameters	(+ve) Mean±SD	(-ve) Mean±SD	P-value
Week@ 0 (Baseline)	Wheals (0/21)	8.06±1.76	8.58±1.12	0.222
	Pruritus (0/21)	7.61±2.34	7.98±2.62	0.162
	UAS-7 total (0/42)	15.67±3.74	16.38±3.12	0.002
Weeks@ 4	Wheals (0/21)	5.85±1.76	6.15±1.88	0.000
	Pruritus (0/21)	5.55±1.14	6.16±2.62	0.002
	UAS-7 total (0/42)	11.4±2.17	12.29±3.22	0.012
Weeks @ 8	Wheals (0/21)	3.29±1.41	3.95±1.86	0.232
	Pruritus (0/21)	2.56±0.18	3.04±0.85	0.000
	UAS-7 total (0/42)	5.81±0.12	6.95±0.62	0.178
Weeks@ 12	Wheals (0/21)	2.3±0.31	3.23±0.52	0.001
	Pruritus (0/21)	2.33±0.36	2.87±0.58	0.285
	UAS-7 total (0/42)	4.65±0.62	6.11±0.33	0.021

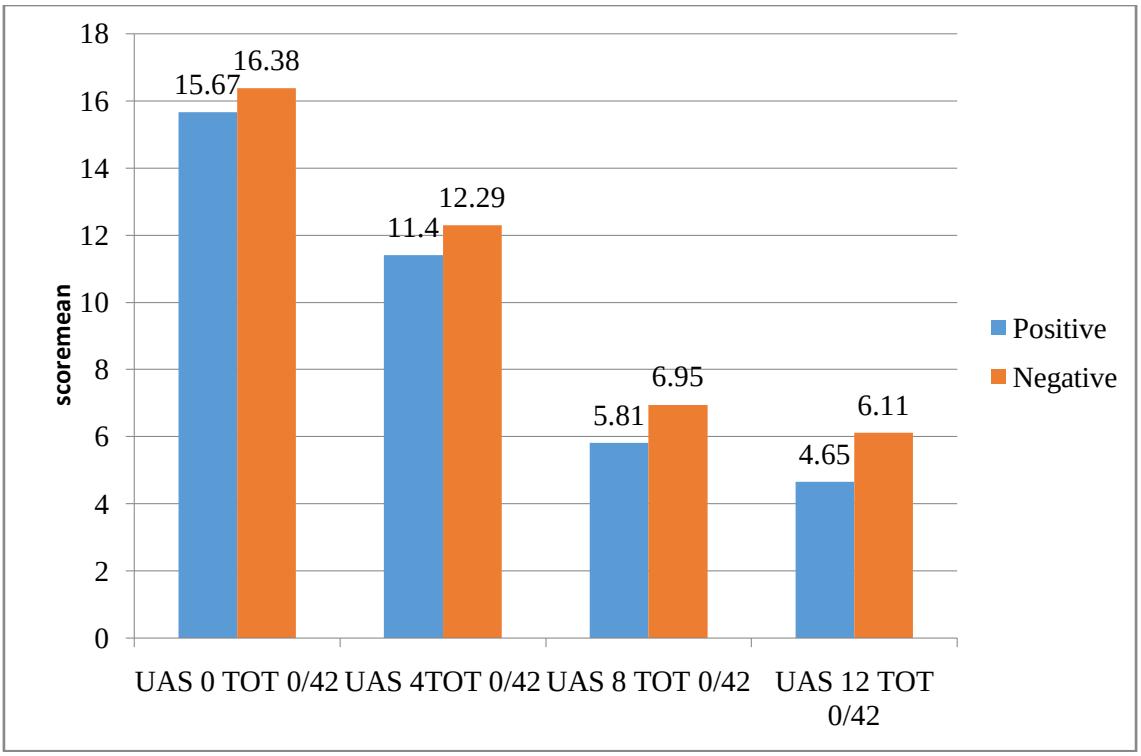


Fig 2:- Comparison of weekly urticaria activity score between study groups.

Table 3:- Percentage of subjects showing >30% improvement in UAS-7 and DLQI score at week 8 and 12 compared to baseline(week @ inception).

Parameters	+ve (n=100)	-ve (n=100)	P-value
UAS 7			
@Baseline	15.67	16.38	≤0.0001
@ 8 weeks	65.52%	61.22%	≤0.0001
@ 12 weeks	70.16%	66.33%	≤0.0001
DLQI			
@Baseline	11.24	11.96	≤0.0001
@ 8 weeks	69.81%	54.28%	≤0.0001
@12 weeks	73.62%	67.42%	≤0.0001

Table 4:- Adverse reactions in the CSU subjects-Logistic regression analysis.

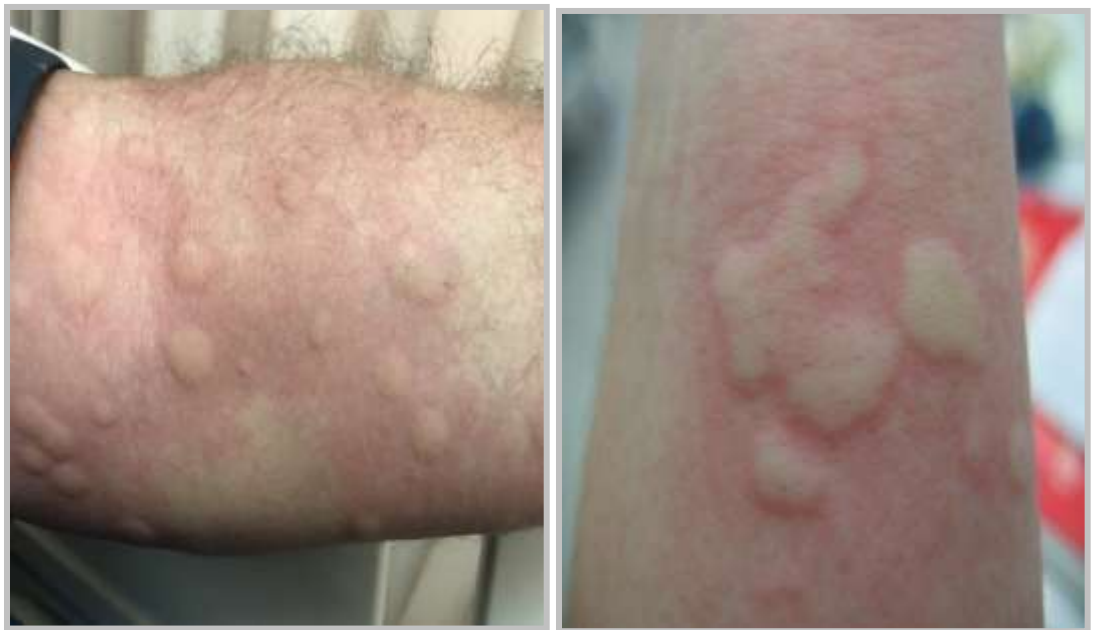
Attributes	+ve (n=100)	–Ve (n=100)	Total
None	90	92	182
Observed	10	08	18

Adverse reaction in the form of mild erythema and pain @ the injection site was observed (9%) in overall subjects with good Specificity (98.11%), Sensitivity (89.56%), PPV(75.42), NPV-(71.24) ,accuracy (80.52) and Odd ratio is >1. There are no serious adverse reactions noticed during the study period.

Table 5:- Comparison of anti-histamine usage at baseline and at 12 weeks between the study groups:

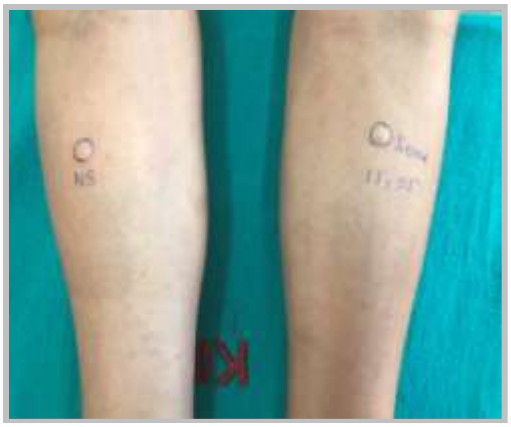
	@ Baseline		@ 12 Weeks	
	+ve	–Ve	+ve	–Ve
Anti-histamine usage				
@Daily two tablets	56	32	14	14
@Daily one tablets	30	50	8	8

@ Alternate day	12	16	12	8
@ Weekly once	2	2	24	30
@ Occasional	0	0	40	40
None	0	0	2	0
Chi-square	10.22 p<0.001		15.62,p<0.01	

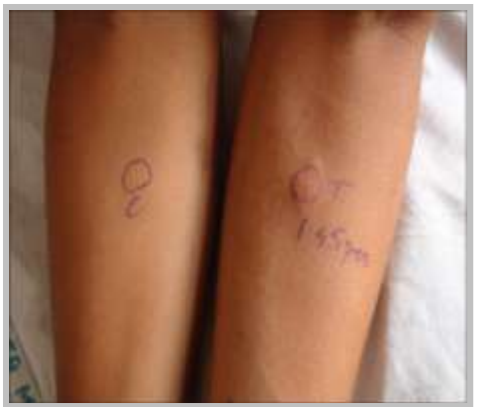


Chronic spontaneous urticaria

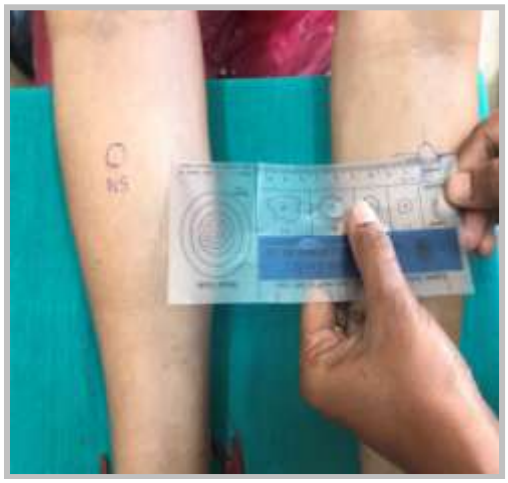
Autologous serum therapy test equipment



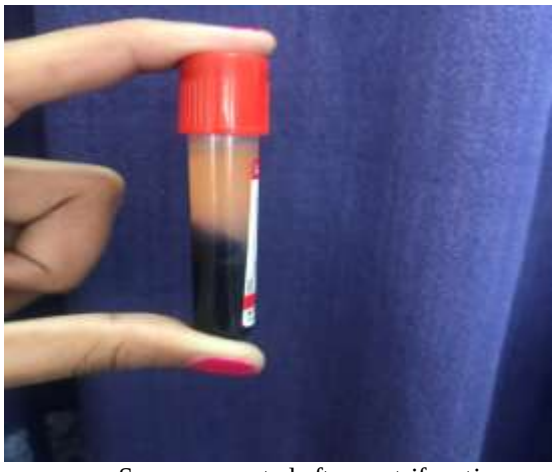
AUtologous serum therapy test



+ve



- Ve autologous serum therapy



Serum separated after centrifugation

Serum for AST

The anti-histamine pill burden @ baseline was higher in +ve than the -ve group. Majority of the cases required @ daily two tablets. Those who required daily two capsules in both groups were significantly improved ($p<0.01$) after receiving autologous serum therapy @ 12 weeks ie the number can reduced for both +ve and the –Ve groups, though the improvement was higher in +ve group (Table 5). Since majority of the CSU subjects has required anti histamines occasionally @ 12 weeks, the efficacy of AST was (40%).

Discussion:-

In the current study, the age range of (26-35) years accounted for the majority of autologous serum therapy (+ve) patients (51%) and was followed by that of (16–25) years (23%). In the case of autologous serum therapy -ve, the age group of 26-35 years (34%) was followed by 16-25 years (31%) in terms of mean age at onset (29.17± 2.14) and (30.62 5.18). In the study by (Kumar et al.), the mean age at onset was (28.54± 13.5) years for the +ve group and (31.55 ±14.43) years for the -ve group. According to (Graltan et al., 2001), the mean age at onset was (33.81± 12.04) years for the positive group and (37.58± 14.36) years for the negative group. According to (Bae et al., 2007), the median age of autologous serum therapy positive patients was 36 years (SD: 17.3 years), while the median age of negative patients was 37 years (SD: 13.4 years). Our study's average age of onset is consistent with other studies. Mean symptom duration was (3.482 1.62) years for the autologous serum therapy +ve group and (2.739 3.73) years for the autologous serum therapy -ve group. According to (Kalpan, 2002), patients with autologous serum therapy positivity had urticaria for an average of 2.5 years, whereas patients with autologous serum therapy negativity had urticaria for a median of 6 months to 10 years. According to (Kumar et al.,) there is no significant difference between the positive and negative groups in terms of the duration of the treatment. As per (Alpay et al.), the positive group duration was 2.97± 5.60 years, while the negative group's was 3.02 ±4.2 years. Such differences are not statistically significant. The group comparisons in our study shows that the duration was longer in the autologous serum therapy positive group than the negative group which is similar to study done by (Bajaj et al).(Kocatur et al., 2012)where as in other studies the duration was slightly more in the autologous serum therapy negative group compared to the autologous serum therapy positive group. In the current study, males (54%) and females (46%), correspondingly of both the total participants in the study. As compared between both the +ve and -ve groups, the affected sample was equal. In both the autologous serum therapy positive and negative groups, our study revealed a male predominance, and it did not co-relate with other studies in terms of the gender distribution of subjects. In our study, urticaria was the only symptom that (92%) of patients reported, whereas (8%) also had angioedema. Angioedema and hives are both common in CSU/CIU patients, with hives accounting for (29–65%) . In a study done by (Vohra et al., 2009) history of atopy was observed (17.10%) in the positive and negative group (21.2%) similar results reported by (Kikuchi et al., 2002) out of 48 CSU ,21 cases had history of atopy 9 cases were autologous serum therapy +ve and 12 cases were autologous serum therapy negative groups. With regard to personal history of atopy, present study showed similarity with other studies. No other relevant co morbidities were found to be significant association with CSU. It is expected that the atopic subjects would belong mostly to be less severe disease subgroup because it has been demonstrated that the atopic subject's trend toward high level of IgE can prevent the binding of anti-FcεR1α antibodies to the receptor, already saturated by immunoglobulin. Both Groups (+ve& -ve) experienced a considerable reduction in urticaria symptoms by the fourth week of treatment, and the control was far better than what could be obtained with on-demand antihistamine use. In both groups, the mean UAS-7 score decreased and the pill load decreased along with the symptom improvement. The positive group experienced a faster and more significant decline in severity during the treatment phase. A similar response was seen in the negative group, and this trend maintained for the next 4 weeks post-therapy in both groups. In the autologous serum therapy positive group, there were (69.81%) of patients who showed more than (30%) improvement in DLQI, compared to (54.28%) in the negative group. In terms of the efficacy metrics utilised (UAS-7 and DLQI) and the number of follow-up weeks, (Vohra et al. 2009) conducted a study that really is comparable to our studies. At the 4th, 8th, and 12th week follow-ups, UAS 7 and DLQI both shown a substantial decline in scores in both groups (autologous serum therapy positive and autologous serum therapy negative), demonstrating the good efficacy of AST in both groups regardless of their auto reactivity. At the end of the follow-up, just (2%) of positive participants needed no antihistamines, while 40% of both autologous serum therapy positive and negative subjects needed them sometimes. Antihistamine use decreased from (100%) baseline in both groups in a research by Bae et al.2007 (37.3%) and (57.1%) in both groups and there is no adverse reaction and mortality noticed in the above study.

Conclusion:-

AST is a helpful adjuvant in people with chronic urticaria that reduces the number of pills needed and enhances quality of life. Many autologous serum therapy -negative patients may also benefit from this method of therapy, and autologous serum skin test reactivity may not properly determine the likelihood of response. Autologous serum therapy positivity probably has a poor concordance with circulating antibodies to IgE or $F_c\varepsilon R_I\alpha$. The effect of nine weekly injections of autologous serum was found to persist even four weeks after cessation of therapy in majority subjects of our study irrespective of auto reactive nature and thus AST finds its place in the therapeutic armamentarium of clinicians treating chronic urticaria. Even though we do not know exactly how or when AST

works but it may prove to be a cheap, effective and potentially curative modality in some patients with recalcitrant chronic urticaria.

Acknowledgement:-

Author acknowledge all Key officers, Dean and Professor and Head of the Department of Dermatology and Venerology , KIMS,Bengalore

Conflict of Interest

There is no conflict of Interest between any funding agency

Ethical clearance

Intuitional ethical clearance was obtained as per the regularity guidelines

References:-

1. Bajaj AK, Saraswat A, Upadhyay A et al. Autologous serum therapy in chronic urticaria: Old wine in a new bottle. Indian J Dermatol Venereol Leprol. 2008; 74:109–13.
2. Vohra S, Sharma N, Mahajan V. Autologous serum skin test: Methodology, interpretation and clinical applications. Indian J Dermatol Venereol Leprol 2009; 75: 545 - 8.
3. Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza BA, Greaves MW. The autologous serum skin test: A screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999; 140: 446-52.
4. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997; 136: 197-201.
5. Kocaturk E, Aktas S, Türkoðlu Z et al. Autologous whole blood and autologous serum injections are equally effective as placebo injections in reducing disease activity in patients with chronic spontaneous urticaria: A placebo controlled, randomized, single-blind study. J Dermatolog Treat. 2012 ;23:465–71.
6. Patil S, Sharma N, Godse K. Autologous serum therapy in chronic urticaria. Indian J Dermatol 2013; 58 (3): 225-226
7. Elias J, Buss E, Kaplan A. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T lymphocytes, monocytes, and mast cells. J Allergy Clin Immunol. 1986;78:914–918.
8. Kaplan A. Clinical practice. Chronic urticaria and angioedema. N Engl J Med. 2002 ; 346:175–179.
9. Bae J-S, Kim S-H, Ye Y-M et al. Significant association of FcεRIα promoter poly- morphisms with aspirin-intolerant chronic urticaria. J Allergy Clin Immunol 2007; 119:449–56.
10. Krupashankar DS, Shashikala K, Rama Madala. Clinical and investigative assessment of patients with positive versus negative autologous serum skin test: A study of 80 south Indian patients. Indian J Dermatol. 2012:57(6).
11. Olwin JH, Ratajczak HV, House RV. Successful treatment of herpetic infections by autohemotherapy. J Altern Complement Med 1997;3:155‑8.
12. Nageswaramma, V. Lakshmi Sarojini, B.Bhavani Pujitha, G.Sirisha, G.Suma Bindu. Efficacy of autologous serum therapy in chronic urticaria. International Journal of Contemporary Medical Research 2017;4(1):110-112.
13. Kumar Y, Bhaskar S, Shankar K. Comparative study of positive versus negative autologous serum skin test in chronic spontaneous urticaria and its treatment outcome. North American Journal of Medical Sciences. 2016;8(1):25.
14. Alpay A, Solak Tekin N, Tekin I, Altinyazar H, Koca R, Çýnar S. Autologous Serum Skin Test versus Autologous Plasma Skin Test in Patients with Chronic Spontaneous Urticaria. Dermatology Research and Practice. 2013;2013:1-6.
15. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. Allergy. 2011;66:317–30.
16. Ganguly S, Vikramkumar A, Kuruvila S. Autologous serum skin test as an indicator of chronic autoimmune urticaria in a tertiary care hospital in South India. Indian Dermatology Online Journal. 2014;5(6):87.
17. Niimi N, Francis DM, Kermani F, O'Donnell BF, Hide M, Kobza-Black A, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106:1001-6.
18. Karn D, KC S. Clinical Outcome of Autologous Serum Therapy in Chronic Idiopathic Urticaria. Journal of Nepal Health Research Council. 2017;15(1):71.
19. Sun L, Erxun K, Li J, Yang J, Han C. Correlations between Anti-Mast Cell Autoantibodies and Chronic Idiopathic Urticaria. Annals of Dermatology. 2014;26(2):145.