Original Research Article

A comparative study of effectiveness of autologus serum therapy with oral antihistamines versus oral methotrexate and oral antihistamines in chronic urticaria patients

Amit Kumar Pandey¹*, Suryakant Ojha¹, Aayushi Mohan², Sunil Prajapati¹

¹Department of Dermatology, BRD Medical College, Gorakhpur, Uttar Pradesh, India
²Department of Dermatology, NRS Medical College, Kolkata, West Bengal, India

Received: 28 August 2019
Revised: 09 October 2019
Accepted: 10 October 2019

*Correspondence:
Dr. Amit Kumar Pandey,
E-mail: amitpandey044@gmail.com

ABSTRACT

Background: Chronic urticaria (CU) is a worrisome problem and patients of CU suffer from the morbidity that arises from irritable itch thus they are subjected to a huge antihistamine pill burden. The symptoms are more prominent in autoreactive urticaria (AU) where auto-antibodies in blood causing recurrent flares. Therefore a need of adjunctive drug to reduce the pill burden is felt need.

Methods: A randomized, controlled study was done. 50 patients were given AST and 50 patients were given oral pulse methotrexate (10-15 mg once weekly) along with levocetrizine in an on-demand basis in both groups. AST was given weekly for nine weeks and followed-up for a total period of 24 weeks. Urticaria total severity score (UTSS) was used to evaluate the effectiveness of treatment. Safety parameters assessed were the spontaneously reported adverse events and laboratory parameters.

Results: UTSS showed significant improvement from baseline, 7th week and 8th week onwards in AST group and methotrexate group respectively. Group comparison showed significant improvement 4th week onwards.

Conclusions: Autologous serum therapy as well as methotrexate both proved effective in chronic urticaria patients. On follow-up improvement is sustained for at least 3-4 months after the last injection in case of AST.

Keywords: Urticaria, Methotrexate, AST

INTRODUCTION

Urticaria is characterized by transient skin or mucosal swellings due to plasma leakage. Superficial dermal swellings are wheals, and deep swellings of the skin or mucosa are termed angioedema. Wheals are characteristically pruritic and pink or pale in the center, whereas angioedema is often painful, less well defined and shows no colour change.¹ It causes a significant decrease in patients quality of life.²³ Lifetime prevalence for urticaria is reported as 7.8-22.3%, with point prevalence being around 1%.²⁴ The risk of developing urticaria in a person is throughout his life is around 15-20%.⁶ The average duration of the disease is around 1-5 years.⁷

Even after extensive investigation the underlying cause remains unknown and so the term idiopathic is used. In many cases thyroid autoimmunity is positive.⁸

Many times urticaria is associated with aggravating factors like diet, drugs, alcohol, viral infections, local
heat and friction, and mental stress and urticaria can be avoided by sampling avoiding these.

There are various treatment options available including antihistamine which is the first line treatment. The second step of treatment is to increase up to four times the standard dose of a second-generation antihistamine.9,11

In refractory cases one can add H2 antihistamines such as cimetidine, famotidine and ranitidine can be added.12 In some cases corticosteroids such as prednisone or prednisolone (0.5 to 1 mg per kg per day) may be added initially to control symptoms.9,13,15

Other drugs that can be used include leukotriene receptor antagonists, such as montelukast and zafirlukast, can also be added, especially in patients with non-steroidal antiinflammatory drugs intolerance or cold urticaria.

Other treatment modalities for controlling refractory urticaria include high-potency antihistamines like hydroxyzine or the tricyclic antidepressant (doxepin) and other immunomodulatory agents like omalizumab and cyclosporine.17,18

Our study compares two such newer modalities autologus serum therapy (AST) and pulse methotrexate dose in controlling urticaria.

METHODS

The present study was carried out in Department of dermatology of tertiary care hospital in Gorakhpur for period of 1 year from January 2017 to January 2018. Ethical committee permission was obtained prior to commencement of study and consent was taken from the patient prior to study. Detailed history and examination was documented in structured proforma.

The study design was prospective interventional study. By systemic random sampling patient were divided into two groups where group 1 received AST and group 2 was given methotrexate 10-15 mg per week. The diagnosis of chronic urticaria (CU) was made clinically.

Baseline investigation performed including complete blood count, liver function test, renal function test, thyroid profile, urine routine and stool routine or microscopy was done.

**Autologous serum therapy**

Five ml venous blood of the patient was drawn with a sterile, disposable syringe from the antecubital vein in sterile BD vacutainer for serum collection. The blood was subjected to centrifugation using centrifuge machine at the rate of 2000 rpm for 10 min at room temperature. 2-ml deep intramuscular injection was given in alternate buttocks or upper arms. Rescue antihistamine was permitted as in the run-in period; no other drugs were permitted.

Thereafter, every week for ten consecutive weeks, 5 ml blood was drawn, serum separated and a 2-ml deep intramuscular injection given in alternate buttocks or upper arms. Rescue antihistamine was permitted as in the run-in period; no other drugs were permitted.

**Inclusion criteria**

Inclusion criteria were patient having almost daily appearance of wheals for ≥6 weeks; patient willing to take part in study and signed written informed consent; patient willing to come for weekly follow up; age between 18 year to 60 year.

**Exclusion criteria**

Exclusion criteria were acute urticarial; pregnant and lactating women; patients suffering from immunosuppression due to drug or disease, advanced diseases of vital organs, on steroids; inability to come for weekly follow-ups; addicted to alcohol or other substance abuse, machinery operators, vehicle drivers and in whom sleep/wake cycle alteration could be an issue; drop outs (patient failed to visit at least thrice during study period in 0, 6 and 10 week).

**Assessment parameters**

**Urticaria total severity score**

With each parameter having a score of 0-3, maximum score being 18.

| Parameters                      | Score         |
|--------------------------------|---------------|
|                                | 0             | 1              | 2              | 3              |
| **Number of wheals**           | None          | ≤10            | 11-50          | >50            |
| **Size of wheals**             | None          | <1 cm          | 1-3 cm         | >3 cm          |
| **Intensity of pruritus**      | None          | Mild           | Moderate       | Severe         |
| **Duration of persistence**    | None          | < 1 hour       | 1-12 hour      | >12 hour       |
| **Frequency of appearance**    | None          | <once or once a week | 2-3 times a week | Daily/almost daily |
| **Frequency of antihistamine use** | None          | <once or once a week | 2-3 times a week | Daily/almost daily |

Table 1: Urticaria total severity score.
Safety parameters

All patients were screened for HIV, HBsAg and VDRL before starting the study.

Proper precaution is taken during handling of blood and serum of the patient.

Clinical adverse events

The adverse events occurring whether or not were considered causally related to study were recorded.

Period of assessment: patients were assessed at 0, 2, 4, 6, 8 and 10 weeks.

Patients were evaluated based upon scores and asked for recurrence and potential side effects. Scores were taken at every visit but for evaluation only scores at start, at end of treatment and at end of 6 months of follow up are taken into consideration.

Statistical method used

Unpaired 't' test was used to compare the data between two groups.

RESULTS

As shown in Figure 1 out of 100 patients, 37 patients were male and rest 63 patients were female. On percentage basis 37% were male and rest 63% were female.

DISCUSSION

The time consuming and frustrating management of CU and associated direct and indirect health costs with socio-economic implications, about 20-30% reduction in performance was assessed.\textsuperscript{19,20} It is well versed in literature that resistant urticaria- a steroid dependent rash is poorly responsive to multiple antihistaminic and immunosuppressive agents.\textsuperscript{21} Okubo et al defined resistant urticaria in patients not responding to 10 mg cetirizine per day for 1 week.\textsuperscript{22} The guidelines by European Union consensus defines- resistant urticaria as the rash which is not controlled after increasing the four times dose of usual dosing of non-sedative H1 antihistamines, but they indicate that this recommendation is based on low quality evidence.\textsuperscript{23}

A study conducted by Sagi et al, with methotrexate it was seen that out of 8 patients with CU who had responded poorly to antihistamines, oral steroids and other immunosuppressants and subsequently treated with weekly 15-25 mg methotrexate, 7 showed complete remission with onset of effect seen at 3-5 weeks, maintained for 2-15 months.\textsuperscript{24} Similarly a study by Perez et al showed 16 patients of steroid dependant chronic
urticaria. Cochrane. Covered by the ST group) only oral antihistamines. The

d A, eieh F, th 2 of methotrexate was noted at periods 2

tended to therapy, 2 were ,

1. REFERENCES

institutional ethic

Ethical approval: The study was appr

Conflict of interest: None declared

Funding: No funding sources

4 months after the last injection.

hrs. On follow up improvement is sustained for at least 3

side effects except local soreness lasting from 12 to

was well

methotrexa

effect of autologous serum therapy as well as

proved effective in

conclusions were drawn: Autologous serum therapy is

given on SOS basis. At the end of the study, following

comparative analysis was carried out in 100 patients of

autologous serum therapy an

The aim of the study was to see effectiveness of

Autohemotherapy (repeated intramuscular injection) is

one of the oldest modalities used in treating urticaria and

other viral or allergen. The mechanism of action is by

inducing tolerance against offending antigen like that in

immunotherapy.

In a study conducted by Bajaj et al it was seen that there is

significant percentage of improvement in CSU patients and

responding really well to autologous serum injection

administration. While in other study AST and autologous

whole blood injections in 88 CU patients did not found

significant difference in terms of improvement between

groups.

In our study we found that patient showed significant

improvement after AST and this improvement was

sustained in follow up period.

CONCLUSION

The aim of the study was to see effectiveness of

autologous serum therapy and oral methotrexate. The comparative analysis was carried out in 100 patients of

CU which were divided into two groups as group 1 (methotrexate group) in which autologous serum therapy was given along with oral antihistamines on SOS basis and in group 2 (AST group) only oral antihistamines given on SOS basis. At the end of the study, following conclusions were drawn: Autologous serum therapy is proved effective in CU patients statistically in group 2, effect of autologous serum therapy as well as methotrexate started appearing 4th week onwards, AST was well-tolerated and none of the patients reported any side effects except local soreness lasting from 12 to 24 hrs. On follow up improvement is sustained for at least 3-4 months after the last injection.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the

institutional ethics committee

REFERENCES

1. Black AK, Grattan CEH. Urticaria. In: Burns DA, Breathnach SM, Cox NH, Griffiths CEM, editors. Rooks Textbook of Dermatology. 8th ed. Blackwell Publishing Ltd; 2010: 22.1-22.39.

2. 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(2):197-201.

3. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. Allergy. 2011;66(3):317-30.

4. Gaig P, Olona M, Munoz Lejarazu D, Caballero MT, Dominguez FJ, Echechupia S, et al. Epidemiology of urticaria in Spain. J Investig Allergol Clin Immunol. 2004;14(3):214-20.

5. Lapi F, Cassano N, Pegoraro V, Cataldo N, Heiman F, Cricelli I, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. Br J Dermatol. 2016;174(5):996-1004.

6. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-72.

7. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-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.

8. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: A study of 90 patients. J Allergy Clin Immunol. 1989;84:66-71.

9. Powell RJ, Leech SC, Till S, Huber PA, Nasser SM, Clark AT. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy. 2015;45(3):547-65.

10. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, et al EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. Allergy. 2009;64(10):1427-43.

11. Ortonne JP. Chronic urticaria: a comparison of management guidelines. Expert Opin Pharmacother. 2011;12(17):2683-93.

12. Fedorowicz Z, van Zuuren EJ, Hu N. Histamine H2-receptor antagonists for urticaria. Cochrane Database Syst Rev. 2012;(3):CD008596.

13. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-7.

14. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69(7):868-87.
15. Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. Ann Emerg Med. 1995;26(5):547-51.

16. de Silva NL, Damayanthy H, Rajapakse AC, Rodrigo C, Rajapakse S. Leukotriene receptor antagonists for chronic urticaria: a systematic review. Allergy Asthma Clin Immunol. 2014;10(1):24.

17. Morgan M, Khan DA. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2. Ann Allergy Asthma Immunol. 2008;100(6):517-26.

18. Mitchell S, Balp MM, Samuel M, McBride D, Maurer M. Systematic review of treatments for chronic spontaneous urticaria with inadequate response to licensed first-line treatments. Int J Dermatol. 2015;54(9):1088-104.

19. Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gimenez-Arnau AM, et al. EAACI/GALEN/EDF/WAO guideline: Definition, classification and diagnosis of urticaria. Allergy. 2009;64:1417-26.

20. Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: A cost analysis of 50 nonimmuno suppressed patients. Arch Dermatol. 2008;144:1417-26.

21. Perez A, Woods A, Grattan CE. Methotrexate: A useful steroid-sparing agent in recalcitrant chronic urticaria. Br J Dermatol. 2010;162:191-4.

22. Okubo Y, Shigoka Y, Yamazaki M, Tsuboi R. Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: A prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life. J Dermatol Treat. 2013;24:153-60.

23. Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gimenez-Arnau AM, et al. EAACI/GALEN/EDF/WAO guideline: Management of urticaria. Allergy. 2009;64:1427-43.