

CLINICAL STUDY

Optimization model research on efficacy in treatment of chronic urticaria by Chinese and Western Medicine based on a genetic algorithm

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strengthening group correlated highly with the pre-treatment total symptom score. The duration of treatment showed the greatest impact on the total symptom score. A quartic equation was established ($y = -1.6403 \times 10^{-6}x^4 + 0.00025576x^3 + 0.0012819x^2 - 1.024x + 79.5879$, and $x = 106.9518$, $y = 83.0036$) using the genetic algorithm.

CONCLUSION: TCM treatment had a better effect in the later stage, whereas WM was better in the early stage. The duration of disease course had an impact on the effects of treatment. If the average total symptom score before treatment was ≤ 83.0036 , TCM or WM treatment could achieve better efficacy.

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Key words: Urticaria; Algorithm; Data mining; Traditional Chinese Medicine; Western Medicine

Abstract

OBJECTIVE: To investigate the potential rules and knowledge of Traditional Chinese Medicine (TCM) and Western Medicine (WM) treatment on chronic urticaria (CU) based on data-mining methods.

METHODS: Sixty patients with chronic urticaria, treated with TCM and WM, were selected. Gray correlation analyses were adopted to determine therapeutic efficacy. Association algorithms were utilized to ascertain the correlation between the disease course and treatment results. A genetic algorithm was applied to discover the optimization model in the TCM and WM treatment on CU.

RESULTS: The total symptom scores after 4 weeks and 8 weeks of treatment in the TCM spleen-

INTRODUCTION

Urticaria is commonly known as "hives". It is a type of localized edema reaction due to the expansion and increased permeability of small blood vessels in the skin and mucous membrane. Manifestations include rapidly developed pale skin and wheals that appear in round or oval shapes. If skin lesions last for >6 weeks this scenario is defined as "chronic urticaria" (CU).¹ The etiology of urticaria is complex and relapse is quite common, so patients often suffer from rashes and itching, which can cause disruption to the activities of daily living. According to Chinese Medicine (CM), the treatments of urticaria include internal therapy, external therapy, acupuncture, and comprehensive internal/external

treatment. In recent years, significant progress has been made in Western Medicine (WM) with respect to the pathogenesis of CU through research on autoantibodies that induce histamine release, as well as genetic and environmental factors. Based on "data mining" methods, we undertook a study to investigate the clinical efficacy of CM and WM for treating CU patients.

MATERIALS AND METHODS

Experimental methods

The diagnosis of CU was based on the definition provided by Zhao in Clinical Dermatology.² Sixty CU patients who visited the Dermatology Department of Shanghai Traditional Chinese Medicine (TCM) hospital from October 2006 to December 2007 were selected. These 60 patients were divided equally into a TCM spleen-strengthening group (TCMSSG) and a WM group (WMG), who were the control group. This study approved by the appropriate ethics committees was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

In the TCMSSG, patients were treated with a prescription [Huangqi (*Radix Astragali Mongolici*) 18 g; 5 red dates; Shanyao (*Rhizoma Dioscoreae Oppositae*) 15 g; Fuling (*Poria*) 12 g; Danggui (*Radix Angelicae Sinensis*) 12 g; Zhishouwu (prepared *Radix Polygoli Multiflori*) 15 g] by decoction, one dose twice a day, over the course of 8 weeks. In the WMG, patients were given cetirizine hydrochloride tablets (10 mg/tablet; Lunan Pharmaceutical Group, Beijing, China), 10 mg/d for 8 weeks. According to the four grading standards mentioned in the European MILOR study,³ we scored the subjective and objective symptoms of CU patients before treatment as well as 2, 4 and 8 weeks after treatment. We then added all the scores together as the total score, and evaluated the efficacy of treatment based on the total score before and after treatment. According to the total symptom score of each patient before and after treatment, the symptom score reduction index (SSRI) was calculated using the following formula.⁴

$SSRI = (\text{pre-treatment total symptom score} - \text{total symptom score after treatment}) / \text{pre-treatment total symptom score}$.

Four levels of efficacy evaluation according to the SSRI were used: $SSRI \geq 0.9$ was classified as "recovered"; $0.6 \leq SSRI < 0.9$ was termed "effective"; $0.2 \leq SSRI < 0.6$ was "progressed"; and $SSRI < 0.2$ was "invalid". The percentage of recovered and cured patients reflected "total efficiency".

CU can be divided into allergic and non-allergic types, most of which is type-1 allergy mediated by immunoglobulin (Ig)E. IgE is a reagent, and its levels in the serum of healthy individuals are negligible, but are significantly increased in those with urticaria.⁵⁻¹⁰ The total IgE count was recorded in CU patients before and after treatment. IgE levels were detected using the rate nephelometry method and the detection reagents were

purchased from Dade Behring (Siemens AG, Berlin, Germany).

Statistical analyses

We used SPSS statistical software (SPSS, Chicago, IL, USA) as described previously.¹¹ The paired t-test was used for the comparison before and after treatment in the IgE group. Analysis of variance was used for the comparison between the two groups after treatment. For further pairwise comparisons, Fisher's least significant difference test was used.

Gray correlation analyses (GRA)

The gray system theory proposes the concept of gray relational grade analyses on each subsystem, and is used to investigate the numerical correlation between the various subsystems (or factors) in a certain way. Therefore, GRA provide a quantitative measure for the development of a system change trend, and are suitable for dynamic process analyses. It is a mathematical model on the degree of correlation between the internal factors of the research system.¹²

The basic idea of GRA is to determine if the sequence of curves are closely correlated. If the two curves are linked closely, the degree of correlation between the corresponding sequences is greater, and vice versa.¹³ Thus, the degree of correlation is a metric of the overall correlation on the sequences. This overall correlation is based on partial correlation, and has a decisive role in the calculation of the degree of correlation. Moreover, a negative correlation is also reasonable and can be shown by a change in the slope of the sequence curves. A Gray similar degree of correlation calculation model is established. This model reflects the negative correlation and simultaneously meets the parallel and is consistent according to the slope differences between the reference sequence and comparative sequence,¹⁴ as defined below.

Set $X_0 = [x_0(1), x_0(2), \dots, x_0(n)]$ as the sequence of the system characteristics.

And $X_1 = [x_1(1), x_1(2), \dots, x_1(n)]$, tem characteristics.

$X_2 = [x_2(1), x_2(2), \dots, x_2(n)]$,

...

$X_m = [x_m(1), x_m(2), \dots, x_m(n)]$ as the relevant factors sequence.

The sequence of the system characteristics and the relevant factors sequence were not equivalent sequences. The order is:

$$\Delta 0(k) = x_0(k) - x_0(k-1), k=2, 3, \dots, n$$

$$\Delta i(k) = x_i(k) - x_i(k-1), k=2, 3, \dots, n$$

$$R0 = \max_i x_0(k) - \min_i x_0(k),$$

$$Ri = \max_i x_i(k) - \min_i x_i(k),$$

$$\text{Correlation degree } \gamma_{0i}(k) = \text{sgn}_k \frac{1}{1 + \left| \frac{\Delta i(k)}{Ri} - \frac{\Delta 0(k)}{R0} \right|}$$

$k = 2, 3, \dots, n; i = 1, 2, \dots, m$. Among them,

if $\Delta i(k) \times \Delta i(0) > 0$, the associated symbolic function $\text{sgnk} = 1$;

if $\Delta i(k) \times \Delta i(0) < 0$, the associated symbolic function $\text{sgnk} = -1$.

$$\xi_{0i}(k) = \frac{1}{n-1} \sum_{k=2}^n \gamma_{0i}(k)$$

Gray relational coefficient

In the present study, the changes in total symptom scores in CU patients upon treatment by Chinese and Western Medicine were analyzed by GRA.

Association algorithm between SSRI and disease course

The association knowledge reflects the interdependent or associated knowledge between an event and other events. The important feature of association rules is "association is naturally combined", which is useful to find the existing mode of all the subsets.¹⁵⁻¹⁷ To understand the correlation between the efficacy of CM and WM treatment and the disease course of the CU patients before treatment, the association rules were used for data mining, with SSRI as the input and the disease course as the output.

Genetic algorithms on optimization modeling

We used a polynomial fitting method to determine the symptoms of CU patients before treatment. We established an equation in which the independent variable was the difference in value of total IgE (after the reduction) before and after treatment, and the dependent variable was the total symptom score of CU patients (after the reduction) before treatment. We used genetic algorithms to explore the potential solution of the equation and analyze the effects of TCM and WM treatments.

RESULTS

Gray similar degree of correlation analyses in the TCMSSG

The data relating to total symptom scores, numerical differences, and degree of correlation in the TCMSSG are shown in Table 1-3.

The gray correlation coefficient was calculated as follows: $\xi_{01}=0.0372$, $\xi_{02}=0.1382$, $\xi_{03}=0.1463$, and the correlation sequence $\xi_{03} > \xi_{02} > \xi_{01}$ was obtained. The total symptom scores after 4 weeks and 8 weeks of treatment in the TCMSSG correlated highly with the pre-treatment total symptom score. That is, after 4 weeks of treatment, the efficacy was much better than in the previous period.

Gray similar degree of correlation analyses in the WMG

The data relating to total symptom scores, numerical differences, and degree of correlation in the TCMSSG are shown in Table 4-6.

The gray correlation coefficient was calculated as fol-

Table 1 Total symptom scores of some CU patients in the TCMSSG

Number	Total symptom score			
	Before treatment	2 weeks after treatment	4 weeks after treatment	8 weeks after treatment
1	75	35	10	0
2	70	45	25	5
3	65	30	10	0
...	...	...	...	...

Notes: CU: chronic urticaria; TCMSSG: Traditional Chinese Medicine spleen-strengthening group.

Table 2 Corresponding numerical differences in the TCMSSG

$\Delta 0(k)$	$\Delta 1(k)$	$\Delta 2(k)$	$\Delta 3(k)$
5	-10	-15	-5
5	15	15	5
5	-15	-15	0
-25	-20	-15	-20
...	...	...	...

Note: TCMSSG: Traditional Chinese Medicine spleen-strengthening group.

Table 3 Degree of correlation in the TCMSSG

γ_{01}	γ_{02}	γ_{03}
-1.0000	-0.9398	-0.9375
0.9231	0.9398	0.9375
-0.9231	-0.9398	0.8571
-0.6667	-0.6240	-0.6977
...	...	...

Note: TCMSSG: Traditional Chinese Medicine spleen-strengthening group.

Table 4 Total symptom scores of some CU patients in the WMG

Number	Total symptom score			
	Before treatment	2 weeks after treatment	4 weeks after treatment	8 weeks after treatment
1	75	65	60	20
2	80	45	30	5
3	65	45	30	30
...	...	...	...	...

Notes: CU: chronic urticaria; TCMSSG: Traditional Chinese Medicine spleen-strengthening group.

lows: $\xi_{01}=0.5958$, $\xi_{02}=0.3905$, $\xi_{03}=0.2933$, and the correlation sequence $\xi_{01} > \xi_{02} > \xi_{03}$ was obtained. The duration of the treatment that showed the greatest impact on the total symptom scores was 2 weeks, next was 4 weeks, and the last was 8 weeks. That is, the effects of WM are complete after 2 weeks of treatment.

Data mining on the association between SSRI and disease course

Inclusion criteria: transient wheal, duration of each attack ≤ 24 h, duration of the course ≥ 6 months, and urticaria symptoms and signs are observed < 24 h before enrollment.¹¹

Table 5 Corresponding numerical differences in the WMG

$\boxtimes 0(k)$	$\boxtimes 1(k)$	$\boxtimes 2(k)$	$\boxtimes 3(k)$
- 5	20	30	15
15	0	0	- 25
- 10	- 10	- 15	10
20	15	10	- 5
...	...	...	...

Note: WMG: Western Medicine group.

Table 6 Degree of correlation in the WMG

γ_{01}	γ_{02}	γ_{03}
- 0.9091	- 0.7925	- 0.9545
0.6667	0.6667	0.8750
0.8333	0.8936	- 0.8400
0.6818	- 0.6240	- 0.6269
...	...	...

Note: WMG: Western Medicine group.

The rules of association in the TCMSSG from strong to weak order were:

- 1) SSRI<0.2463→ disease course ≥48 months;
- 2) SSRI=0.2463 - 0.5509→ disease course ≥48 months;
- 3) SSRI=0.6692-0.9064→disease course=12-14 months.

The rules of association in the WM group from strong to weak order of the four rules were:

- 1) SSRI <0.2728→ disease course ≥48 months;
- 2) SSRI=0.2728 - 0.5444→ disease course ≥48 months;
- 3) SSRI=0.6523 - 0.8683→ disease course <6 months;
- 4) SSRI=0.5444 - 0.6523→ disease course <6 months.

IgE levels in the TCMSSG and WMG

Comparison of the total levels of IgE in serum before and after treatment in the two groups revealed the differences to be statistically significant (all $P<0.01$). After treatment, the total IgE levels in the TCMSSG were significantly lower than those in the WMG ($P=0.005$) (Table 7).

For the IgE group before and after treatment, a paired t -test was used; for comparison between the two groups after treatment, analysis of variance was employed; for further pairwise comparisons, the least squares difference test was used. Normal reference range: IgE <150 IU/mL.

Relation equation and genetic algorithms

We established a quartic equation according to the data of Table 8:

$$y = -1.6403 \times 10 - 6x^4 + 0.00025576x^3 + 0.0012819x^2 - 1.024x + 79.5879.$$

This relation equation is non-linear, and has no conventional method to obtain the exact solution.¹⁸ Searching for the optimal solution of the relation equation involves the application of an evolutionary algorithm,

Table 7 Total IgE levels before and after treatment in the TCMSSG and WMG (IU/mL, $\bar{x} \pm s$)

Group	n	Before treatment	After treatment	Difference
TCMSSG	30	183±91	78±20	105±81
WMG	30	170±85	99±35	71±68

Notes: TCMSSG: Traditional Chinese Medicine

spleen-strengthening group; WMG: Western Medicine group.

such as a genetic algorithm, immune algorithm and particle swarm optimization.¹⁹ We used a genetic algorithm and selected 10 as the number of individuals in the population, a binary encoding length of 20, a cross-over probability of 0.95, mutation probability of 0.08, and 10-6 as the accuracy. Calculated: $x=106.9518$; $y=83.0036$. That is, whether CU patients were treated with TCM or WM, if the average difference in total IgE before and after treatment was 106.9518, the approximate maximum value in the average value of the total symptom score before treatment was 83.0036.

DISCUSSION

Data mining can be incomplete, noisy, fuzzy or random data. Data mining is a decision support process. In the present study, it can be used to "dig out" potential modes and predict the behavior of TCM and WM treatment as well as to help physicians make the correct judgment on the treatment effect (and thereby reduce ineffective behaviors and processes and acquire greater efficacy). Therefore, "data-warehouse" and data-mining methods and their applications provide an evidence-based, decision-making technical basis to the treatment of CU using TCM and WM. Data-mining methods have been used in medicine to analyze the effects of treatment, such as application of composite data-mining methods to study acupuncture in juvenile myopia.¹⁵

According to the results of the Gray similar degree of correlation analyses, if the patient did not recover after 8 weeks of TCM treatment, extending therapy may be of some benefit. However, for WM treatment, if the symptoms did not improve after 2 weeks, other treatments should be considered.

The data-mining results of the two groups on association knowledge between the SSRI and disease course suggested that, the greater the SSRI (tends to 1), the shorter the disease course of CU patients. That is, the duration of the disease course has a certain impact on the effect of treatment.

A genetic algorithm is a search heuristic that mimics the process of natural evolution. In the genetic algorithm, the optimal solution (or near-optimal solution) was searched in a feasible space via coding, selection, crossover, and mutation. After the analysis of the genetic algorithm, if the pre-treatment total symptom score was >83.0036, to get a better therapeutic effect, the physician can choose other treatment methods, such as

Table 8 Total symptom scores and Δ total IgE values before and after treatment after reduction (IU/mL)

(After reduction) before-treatment total symptom score	55	60	65	70	75	80	85
(After reduction) Δ total IgE (IU/mL) after treatment	28.85	23.28	71.62	124.54	89.66	110.27	115.54

medicinal bathing or acupuncture. For CU patients with a total symptom score <83.0036 , the TCM and WM treatments mentioned in here could achieve the desired effects.

In summary, 60 patients with CU treated by TCM and WM were selected. The Gray similar degree of correlation analyses, association algorithm and genetic algorithm in data mining were adopted to analyze the effects of TCM and WM in CU patients. TCM treatment had a better effect at a later stage, whereas WM was better in the early stage. The duration of the disease course had an impact on the effect of treatment. If the average total symptom score before treatment is ≤ 83.0036 , TCM or WM treatment can achieve better efficacy.

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