Archives of Dermatological Research (2019) 311:801–805
https://doi.org/10.1007/s00403-019-01967-0

ORIGINAL PAPER

Effects of combination of mizolastine and proteoglycan on chronic urticaria: a randomized controlled trial

Xing Xiong[1] · Liping Song[2] · Fangru Chen[1] · Xiaoli Ma[3]

Received: 22 April 2019 / Revised: 21 July 2019 / Accepted: 16 August 2019 / Published online: 27 August 2019

Abstract

The present study aimed to observe the therapeutic effect of combined mizolastine and proteoglycan in chronic urticaria. The patients were randomly divided into the treatment group ($n=56$) and the control group ($n=44$). The treatment group was medicated with calcium gluconate (10 mg/ time, 1 time/day), vitamin D3 (intramuscular 10 mg/time, 1 time/week), mizolastine (10 mg/time, 1 time/day), and proteoglycan (1.2 g/time, 3 times/day), while the control group was administered with the same drugs except proteoglycan for 4 weeks. After treatment with combined mizolastine and proteoglycan, therapeutic effect with symptoms decline index (SDI) more than 60% was significant different (44 vs. 24, $p=0.000973$) and the relapse rate after 2 months was significantly lower (17.9% vs. 38.6%, $p=0.0202$). Using ELISA, we found that the IFN-γ (37.88 ± 4.27 pg/mL vs. 21.91 ± 4.95 pg/mL, $p=0.028$) levels were specifically increased in the experiment group. The combination of mizolastine plus proteoglycan is effective in treating chronic urticaria with better therapeutic effect and lower relapse rate through promoting IFN-γ production.

Keywords Chronic urticaria · Cell-mediated immunity · IL-4 · Interferon-γ

Introduction

Chronic urticaria is a set of unique and heterogeneous skin disease and a common allergic skin disease characterized by repeated attacks, lasting over 6 months to years and difficulty in curing. According to World Allergy Organization (WAO) guidelines, chronic urticaria is defined as the occurrence of hives/weals with or without angioedema for 6 weeks or more due to known and unknown causes. The main symptom of urticaria is pruritus due to histamine, one of the best-characterized pruritogens in humans [1]. Though several mediators are involved in urticaria, histamine released from mast cells play a key role. Because of the continuous clinical symptoms such as itching, wealing, and unpredictable course of the disease, the patient's personal daily activities (work, study, sleep, housework) and emotional and social activities, etc. are affected and results in severe impairment in the quality of life. Currently, H1 receptor antagonists are widely used for treatment of urticaria [2]. However, there are still a lot of patients with chronic urticaria who do not tolerate or get benefit from the therapy and who require effective treatment.

Many etiologies have been implicated in the causation of chronic urticarial, but an imbalance between cytokines and T lymphocyte subgroups may be involved in it. $CD8^+$ T lymphocyte is a cell with killing activity. It can kill target cells by secreting cytokines such as TNF, granulase and perforin, mediating target cell apoptosis [3]. $CD4^+$ T cells can differentiate into two different functional subgroups after being activated by antigen presented: Th1 and Th2. Th2 cells can release cytokines such as interleukin 4, 5, and 10, inducing activation of B lymphocytes and macrophages and subsequent releases of IgE and histamine and leading to chronic urticaria [4]. Th1 cells can release cytokines such as IFN-γ and interleukin-12, slowing down the occurrence of hypersensitivity and the differentiation of Th cells into Th2 cells and alleviating the clinical symptoms of chronic urticaria [5]. Autoimmune diseases, such as lupus erythematosus,

✉ Liping Song
weihongtujn@sina.com

[1] Dermatological Department, Affiliated Hospital of Guilin Medical University, Guilin 541001, Guangxi, China

[2] Department of Epidemiology and Health Statistics, School of Public Health, Guilin Medical University, No. 109 North Second Road, Huancheng, Qixing District, Guilin 541001, Guangxi, China

[3] School of Transportation, Chongqing Jiaotong University, Chongqing 404100, China

Sjogren's syndrome, rheumatism, thyroiditis and hyperthyroidism, and allergic asthma, are closely related to the occurrence of chronic urticaria [6–8], suggesting that immune imbalance may be one of the key factors for the occurrence and development of chronic urticaria.

Therefore, antihistamines and immune modulators are necessary for the treatment of urticaria. Mizolastine is second generation, non-sedating, fast, long acting H1 receptor antihistamine, and the first-line drug for chronic urticaria [9]. It inhibits the release of histamine from activated mast cells, the chemotaxis of inflammatory cells, and the expression of intercellular adhesion molecule-1 during allergy [10]. Chronic urticaria patients have low serum calcium levels. Calcium gluconate and vitamin D3 supplementation in combination with antihistamine showed elevated response in resolving the symptoms of chronic urticaria [11]. Proteoglycan is a polysaccharide and sulfated polysaccharide isolated from the algae and spirulina, which can reduce the inflammatory response and hypernociception in mice by reducing neutrophil migration and cytokines concentration [12]. It also acts as a potent immune-regulatory drug during immune deficiencies [13]. In our present study, we examined a new therapy by combination anti-histamine drug mizolastine and immune-regulatory drug proteoglycan to treat chronic urticaria.

Materials and methods

Clinical data

Before the experiments, we obtained approval for our study from the Ethics Committee of Guilin Medical University and written informed consent from all participants involved in our study. Inclusion criteria included: (1) the patients aged 18–65 were diagnosed as chronic urticaria with a course over 6 weeks and at least 2 times of symptom onset per week and (2) the patients could complete the treatment and sign the informed consent. Exclusion criteria: (1) patients with the application of glucocorticoid and immunosuppressants or immune modulators in recent 2 weeks; (2) patients with the application of antihistamine drugs in recent 1 week; (3) patients with allergy to Mizolastine; and (4) patients with severe cardiovascular, liver and kidney diseases, malignant tumors, autoimmune diseases, chronic infectious diseases, etc. One hundred cases of patients with chronic urticaria between Sep 2015 and Sep 2016 in our hospital were chosen and divided into the treatment group ($n = 56$) and control group ($n = 44$) according to random number table method. The trial is a double-blind, randomized, single-center study. Each patient was not aware of the specific content of the drugs. In addition, the treatment and data analysis were performed by different researchers.

The method of treatments

The patients in the treatment group were medicated with calcium gluconate tablets (10 mg/ time, oral 1 time a day); Proteoglycan (1.2 g/time, 3 times/day); Mizolastine (10 mg/ time, 1 time/day); and Vitamin D3 (intramuscular 10 mg/ time, 1 time per week), while the patients in the control group were medicated with the same drug and dosage except proteoglycan. Proteoglycan tablets (0.3 g × 12 tablets × 4 plates/boxes) are purchased from Fuzhou Hai Wang Jin Xiang Traditional Chinese Medicine Co., Ltd, Fujian, China. All medications were administered to both groups for 4 weeks with right dose on time. Liver, kidney, and blood and urine routine examination were checked before and after the treatment. At the end of the treatment, clinical therapeutic effect was evaluated and adverse reactions were recorded. Follow-up was carried out to 2 months after treatment and relapses were recorded.

Assessment of therapeutic effects

To assess the therapeutic effects of chronic urticaria, the three features of urticaria including itching, erythema number, and erythema size were recorded and scored according to urticaria activity score (UAS) as following: (1) itching: no itching, mild itching (does not affect the normal life and work), medium itching (tolerable), and severe itching (significantly affect the normal life and work) were scored as 0, 1, 2, and 3, respectively; (2) erythema number: no erythema, skin lesion < 10, skin lesion between 10 and 25, and skin lesions > 25 were scored as 0, 1, 2, and 3, respectively; (3) erythema size: no erythema, diameter < 1.5 cm, diameter of 1.5–2.5 cm, > 2.5 cm in diameter were scored as 0, 1, 2, and 3, respectively. Total scores of clinical symptoms were obtained according to the above three items [14]. The therapeutic effect was assessed according to the symptoms decline index (SDI): (total scores before treatment − total scores after treatment)/total scores before treatment × 100%. Efficacy was classified on the basis of SDI such as SDI 90% or higher, cure; SDI 60–89%, powerfully; SDI 20–59%, effectively; SDI < 20%, void; SDI fell below 60% after marked improvement, relapse.

ELISA

Venous blood was collected from the patients and interleukin(IL)-4, 17, IFN-γ, and TGF-beta 1 secretion in serum were examined with rat anti-human enzyme-linked immunosorbent assay kits (Rapidbio, Columbia, CA, USA) according to the manufacturer's instructions. The plates were tested using an automatic quantitative microtiter plate reader

(BioTek ELX800, USA) at a 450 nm to read absorbance value. The cytokines levels were determined according to a standard curves.

Statistics

SPSS 10.0 software was used to analyze data. Statistical comparisons between control and treatment groups were performed using the student *t* test for continuous variables and either the X^2 or Fisher exact tests were used for categorical variables. PASS software was used to calculate the sample size of the two groups by setting $\alpha = 0.05$, $\beta = 0.10$, which meet the test requirements. $P < 0.05$ was recognized as statistically significant.

Results

Combination of mizolastine and proteoglycan promotes therapeutic effect

A total of 155 patients were screened and divided into the treatment group and control group according to random number table method. Fifty six in the treatment group and forty four in the control group were actually enrolled. Two groups of patients had no statistically significant differences ($p > 0.05$) in gender, age, duration, etc. (Table 1).

After treatment with the combination of mizolastine and proteoglycan for 4 weeks, the therapeutic effects were markedly better. Fifty-six patients in treatment group with had an average UAS of 7.53 ± 0.84 before treatment and 0.64 ± 0.21 after treatment, while 44 patients in the control group had an average UAS 7.41 ± 0.93 before treatment and 1.83 ± 0.28 after treatment. There was a significant difference in efficacy between the two groups ($r = 2.89$, $p < 0.01$). The therapeutic effect was further assessed according to the symptoms decline index (SDI) with cure (SDI > 90%), powerfully (SDI 60–89%), effectively (SDI 20–59%), and void (SDI < 20%) [15]. The results showed that the effectiveness (%) including cure ($n = 31$) + powerfully ($n = 13$) + effectively ($n = 5$) was 87.5% in the experimental group, and the effectiveness (%) including cure ($n = 16$) + powerfully ($n = 8$) + effectively ($n = 10$) was 77.3% in the control group. Although there were no differences in effectiveness rate between the two groups ($p = 0.1765$), the difference in therapeutic effect with SDI more than 60% including cure + powerfully was significant (78.6% vs. 54.5%, $p = 0.000973$, Table 2).

Combination of mizolastine and proteoglycan promotes IFN-γ production

Using ELISA, there were no significant differences in cytokine levels between experiment and control groups before treatment. However, after treatment, the IFN-γ ($p = 0.036$) levels were significantly increased, while TGF-beta 1 ($p = 0.028$) significantly decreased when compared with patients before treatment in the experimental groups. While in the control group, only TGF-beta 1 ($p = 0.034$) significantly decreased when compared with patients before treatment, indicating proteoglycan specifically promoting IFN-γ production in patients (Table 3).

Adverse effect

There were no deaths or serious adverse reactions in this study. Two groups of patients had general adverse reactions such as drowsiness, dizziness, dry mouth, and nausea. Nine cases (16.0%) in experimental group and 12 cases (27.3%) in control group were reported adverse reactions, and they became normal after drug withdrawal. The incidence of the adverse events had no statistical significance between the two groups ($p = 0.172$, Table 2).

Table 1 Characteristics of participants

Groups	Patients screened	Patients enrolled	Male	Female	Average age (y)	Average course (m)
Treatment group	85	56	25	31	35.45 ± 12.11	16.34 ± 10.76
Control group	70	44	19	25	34.97 ± 13.76	15.89 ± 11.67

Table 2 Evaluation of therapeutic effects

Groups	Cure	Powerful	Effective	Void	SDI > 60%	Effectiveness (%)	Relapse (%)	Adverse reaction (%)
Treatment group ($n = 56$)	31	13	5	7	78.6	87.5	17.9	16.0
Control group ($n = 44$)	16	8	10	10	54.5	77.3	38.6	27.3

Table 3 IFN-γ, IL-4, IL-17, and TGF-β1 were assayed by ELISA

Cytokines	Control group ($n=44$)		Treatment group ($n=56$)	
	Before treatment	After treatment	Before treatment	After treatment
IFN-γ (pg/mL)	22.71 ± 4.12	16.33 ± 3.49	21.91 ± 4.95	37.88 ± 4.27*
IL-4 (pg/mL)	3.11 ± 0.65	4.27 ± 0.98	3.05 ± 0.66	5.93 ± 0.92
IL-17 (pg/mL)	119.45 ± 17.34	122.33 ± 16.45	121.43 ± 16.23	129.43 ± 16.55
TGF-β1 (pg/mL)	897.85 ± 54.19	634.98 ± 61.05*	904.42 ± 672.56	603.45 ± 38.09*

*$p < 0.05$ vs. before therapy

Combination of mizolastine and proteoglycan decreases relapse rate

Relapse rate was 17.9% (10 cases) in treatment group and 38.6% (17 cases) in control group after 2 months ($p=0.0202$, Table 2). The difference was statistically significant.

Discussion

Chronic urticaria is a common skin allergic disease. Its etiology and pathogenesis is relatively complex and mainly induced by lgE-mediated humoral immune system. Psychological stress, cold temperature, or vibration is the triggering factor for chronic urticaria. Mizolastine is a specific selective histamine H1 receptor antagonist which inhibits arachidonic acid and other inflammatory factors. It competitively inhibits histamine H1 receptor [16]. Clinical trials showed that the mizolastine a rapid, safe and potent antihistamine with a response rate to chronic idiopathic urticaria 74.1% [17]. The results of this study also showed that the effective rate of mizolastine was 77.1%, which was consistent with the previous report. Moreover, calcium is routinely administered to urticaria patients, because chronic urticaria patients had low serum calcium levels and revealed a calcium dependent inhibition of histamine release [11, 18]. Though the therapeutic effect is positive, single therapy with antihistamines for the treatment of chronic urticaria appears resistant. Therefore, it is needed to combine mizolastine with other drugs to increase the efficacy for the treatment of chronic urticaria.

According to the previous study, it was concluded that the pathogenesis of chronic urticaria involves both humoral as well as cell-mediated immunity. Many immune modulators can modulate immune imbalance such as bacterial preparation and glycoprotein [19]. Proteoglycan is a kind of polysaccharide or sulfated polysaccharide isolated from the algae and spirulina. Several reports showed that Proteoglycan is suggested to bridge innate and adaptive immunity due to its' ability to regulate neutrophil, macrophage, T and B lymphocyte, and dendritic cells activities [20, 21]. Thus, the administration of the Proteoglycan is suggested to facilitate immune sensing and enhance T-cell-activating immunotherapies.

In the present study, a randomized controlled observation was done in 100 cases. After observation, it was found that the therapeutic effect was better in treatment group vs. the control. After 2 months of follow-up, it was found that the relapse rate in the treatment group was lower than that in control group. Moreover, the IFN-γ levels were specifically increased after treatment treatment the experiment group. However, there are several limitations in the present study. First, we did not classify the patients with chronic urticaria, which has many types and complicated etiologies. In addition, the purpose of our study is to investigate the benefits of immune modulators in the treatment of chronic urticaria, so the study's sample size is relatively small. Moreover, the effects of proteoglycan on skin tissue immune function in patients also need further study. However, according to the effect of clinical response, the immune modulators will have a good application prospect in the future clinical treatment of chronic urticaria.

Conclusion

The combination of mizolastine and proteoglycan is effective in treatment of chronic urticaria with better therapeutic effect and lower relapse rate through specifically promoting IFN-γ production.

Funding The study was supported by National Natural Science Foundation Regional Science Fund Project (81360441); Guangxi health department fund project (S201316-09); Guangxi education department fund project (2013 YB165).

Compliance with ethical standards

Conflict of interest Xing Xiong declares that he has no conflict of interest. Liping Song declares that she has no conflict of interest. Fangru Chen declares that she has no conflict of interest. Xiaoli Ma declares that she has no conflict of interest.

Ethical approval The protocol was approved by Ethics Committee of Guilin Medical University (Permit Number: GMU-1100012-7). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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