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Original Article

Acupuncture combined with pricking and cupping therapy is effective in patients with chronic spontaneous urticaria

Yu Shi[1*], Haichao Guo[1*], Yuzhu Du[1], Jin Wang[2], Yan Shang[3], Yanjun Wang[1]

[1]Department of Acupuncture and Moxibustion, The First Affiliated Hospital of Hebei College of Traditional Chinese Medicine, Shijiazhuang 050011, Hebei, China; [2]Department of Oncology, Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine, Beijing 100000, China; [3]Department of Neurology, Dingzhou Hospital of Traditional Chinese Medicine, Dingzhou 073000, Hebei, China. [*]Equal contributors.

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Abstract: Objective: To determine the effects of acupuncture combined with pricking and cupping therapy on the balance of Th1/Th2 cytokines in patients with chronic spontaneous urticaria (CSU). Methods: The medical records of 75 patients with CSU treated in The First Affiliated Hospital of Hebei College of Traditional Chinese Medicine from January 10, 2021 to January 10, 2022 were collected and analyzed retrospectively. Among them, 35 patients treated with traditional therapy were assigned to a control group, and 40 patients treated with acupuncture combined with pricking and cupping therapy to an observation group. The clinical efficacy and adverse reactions in the two groups were compared after therapy. The two groups were also compared in terms of the levels of immunoglobulin (Ig)-E, interleukin (IL)-4 and interferon-γ (INF-γ) before and after therapy. In addition, the visual analogue scale (VAS) for pruritus was adopted for recording the pruritus degree of patients before and after therapy. The Dermatology Quality of Life Index (DLQI) was adopted to compare the quality of life between the two groups before and after therapy. The Hamilton anxiety scale (HAMA) and Hamilton depression rating scale (HAMD) were adopted for comparison of the anxiety and depression between the two groups before and after therapy. Moreover, the Pittsburgh sleep quality index (PSQI) was used to compare sleep quality between the two groups before and after therapy. Results: The control group showed a significantly lower total response rate than the observation group ($P<0.05$). Compared with the control group, the observation group showed significantly lower levels of IgE and IL-4, and a higher IFN-γ level and had significantly lower pruritus-VAS, DLQI, HAMA, HAMD and PSQI scores ($P<0.05$). Additionally, the two groups were not greatly different in adverse reactions (nausea, sleepiness, ecchymosis and dizziness) ($P>0.05$). Conclusion: Acupuncture combined with pricking and cupping therapy is highly effective in CSU, because it can significantly alleviate the symptoms as well as negative emotions, and improve the quality of life, sleep quality and the balance of Th1/Th2 cytokine in patients.

Keywords: Acupuncture, pricking and cupping therapy, chronic spontaneous urticaria, Th1/Th2 cytokine

Introduction

Urticaria is a recurrent allergic skin disease, with itchy patches and pruritus as the primary manifestations, accompanied by (or without) angioedema, which can subside within 24 hours after occurrence of each itchy patch, and chronic urticaria is determined when the recurrence lasts for more than 6 weeks [1]. Urticaria can be classified into chronic induced urticaria and chronic spontaneous urticaria (CSU) according to its incidence, and CSU is most common [2]. CSU is a skin disease that, without obvious inducement, spontaneously forms reddish itchy patches and pruritus with angioedema [3]. According to an epidemiological survey, CSU accounts for over 60% of chronic urticaria in China, and women are a high-risk population [4]. For patients with CSU, the clinical symptoms are commonly found on the upper and lower limbs, and worsen in summer and at night. Because of the long course of disease and various inducements of CSU, it has a high recurrence and causes high medical expenses,

which greatly compromises the patients' physical and mental health as well as quality of life [5].

Modern medicine believes that CSU is related to human autoimmunity and is driven by skin mast cells. Histamine is the main vector of urticaria. Serum immunoglobulin (Ig)-E, as the main antibody to type I allergy, is mediated by functional autoantibodies against high affinity IgE receptors or IgE autoantibodies against autoantigens [6]. Currently, there are routine treatment drugs including antihistamines, hormones, immunosuppressants and antidepressants which are used in clinical practice [7]. However, long-term medication of these drugs will trigger tolerance in patients. Research has shown that the median tolerance of antihistamines is 3 years, and insufficient treatment will inevitably lead to disease recurrence [8]. Additionally, long-term oral administration of drugs can also lead to adverse reactions such as headache, lethargy, fatigue, dry mouth and allergy [9]. Therefore, it is urgent to explore new therapeutic regimens for CSU.

Adverse drug reactions often plague CSU patients, so it is particularly important to actively seek non-drug therapy with definite curative effect [10]. As a representative of non-drug therapy, the ancient acupuncture technique has been extensively adopted. According to prior studies, acupuncture can improve the phagocytosis of macrophages through nerve cells and body fluids, as well as shorten the production time of related antibodies, increase the content of related antibodies, and prolong their action time in the blood, so as to regulate the immune function of the human body to maintain the dynamic balance of immune function, and then cure the disease [11, 12]. Pricking and cupping therapy, a therapy in Traditional Chinese Medicine (TCM), is a compound therapy based on pricking and bloodletting therapy, combined with cupping. Clinically, sterile needles such as three-edged needles are usually used to quickly puncture the skin or superficial veins of local acupoints to release the proper amount of blood, and cupping is used locally in the meantime [13]. Prior research has revealed that pricking and cupping therapy can be used not only for empirical and heat syndrome, but also for pain syndrome, blood stasis, especially stubborn and chronic diseases [14]. Whereas, there is no relevant research on whether acupuncture combined with pricking and cupping therapy has a therapeutic effect on CSU patients.

Accordingly, this study analyzed the therapeutic effect of acupuncture combined with pricking and cupping therapy on CSU patients and its influence on patients' immune function.

Methods and data

Clinical data

The medical records of 75 patients with CSU treated in The First Affiliated Hospital of Hebei College of Traditional Chinese Medicine from January 10, 2021 to January 10, 2022 were collected and analyzed retrospectively. Among them, 35 patients treated with traditional therapy were assigned to a control group, and 40 patients treated with acupuncture combined with pricking and cupping therapy to an observation group. This study was performed with the approval from the Medical Ethics Committee of The First Affiliated Hospital of Hebei College of Traditional Chinese Medicine, with ethical approval number of 2018-KY-023.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the international criteria of definition, classification, diagnosis and management of urticaria [15], patients with normal routine blood and liver and kidney function examination results, patients who had not received antihistamines within 1 week before therapy and who had not taken non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants within 1 week before therapy, and those with detailed clinical data.

Exclusion criteria: Pregnant women, women who planned pregnancy, patients with a history of alcohol allergy or drug abuse, patients with infectious skin diseases, or serious skin damage, breakage, infection, ulcer, or scar at the pricking and cupping parts or acupoint for catgut implantation, patients who were allergic to the drugs in this clinical study, patients diagnosed with malignant tumor, hemophilia, thrombocytopenia or other spontaneous hemorrhagic tendencies, patients with dysfunction of absorption or repair in skin or subcutaneous

tissue triggered by other diseases, patients with severe cardiovascular or cerebrovascular diseases, patients with central nervous system diseases or mental diseases, and patients in active stages of tuberculosis.

Therapeutic regimens

For the control group, the patients were orally treated with cetirizine hydrochloride tablets (Shandong Sibangde Pharmaceutical Co., Ltd., State Food and Drug Administration approval number: H20084632), once a day, 10 mg a time, with 10 consecutive days as a treatment course. The efficacy in the patients was evaluated after three courses of continuous treatment, with an interval of 2-3 days between each course.

The observation group was intervened by pricking and cupping therapy. The acupuncture points Quchi (double), Hegu (double), Zhongwan, Tianshu, Guanyuan, Xuehai (double), Zusanli (double), Yinlingquan (double), and Sanyinjiao (double) were selected. The patient was instructed to take a prone position, so that the operation site can be fully exposed. The skin for operation was routinely disinfected. A 0.30 mm×40 mm disposable Hwato aseptic acupuncture needle (manufacturer: Suzhou Medical Appliance Factory, production license No.: SSYJX 20010020) was adopted. First, straight acupuncture was performed at bilateral Zusanli and Sanyinjiao (30-60 mm), and the twirlingreinforcing needling method was conducted for 60 s. Then straight acupuncture was performed at Zhongwan (20-40 mm) and the twirling-reinforcing needling method was conducted at a small amplitude and high frequency for 60 s. The needle was inserted into the bilateral Quchi (30-50 mm), and the twirling-reinforcing needling method was used for 60 s. The normal acupuncture treatment was applied to the Hegu, Tianshu, Guanyuan, Xuehai, Yinlingquan, and needles were retained for all acupoints for 25 min. Then the patient was required take a prone position to expose the skin on his back. Dazhui and Geshu (double) acupoints were selected. After routine disinfection, the above points were punctured successively with a blood collection pen (Jiangmen Xinli Medical Apparatus and Instruments Co., Ltd., batch number: XL-020-1).

Each point was punctured 5 times, with the needle tip penetrating the skin as the depth, and then cupping was conducted immediately and retained for 10 min, with bleeding of about 2 ml per point as the criterion. At the end, the skin was cleaned with aseptic dry cotton balls and the patient was required to avoid the cold, water bath and so on for the skin. The above two methods were used in combination, both once every other day, for a total of 12 times, as a course of treatment.

Enzyme-linked immuno-sorbent assay (ELISA)

The serum levels of Ig-E (EK175), interleukin (IL)-4 (EK104) and interferon-γ (INF-γ, EK180) were detected via ELISA, with kits from Hangzhou Lianke Biotechnology Co., Ltd. The operation steps were conducted in strict accordance with guidelines of the kits.

Outcome measures

Primary outcome measures: The Clinical efficacy of the two groups was compared. The levels of IgE, IL-4 and IFN-γ in the two groups were compared before and after therapy.

Secondary outcome measures: The adverse reactions were compared between the two groups after therapy. The visual analogue scale (VAS) for pruritus was adopted to record the pruritus degree of patients before and after therapy [16]. The Dermatology Quality of Life Index (DLQI) was adopted to compare the quality of life between the two groups before and after therapy [17]. The clinical data were also compared between the two groups. The Hamilton anxiety scale (HAMA) and Hamilton depression rating scale (HAMD) were adopted to compare the anxiety and depression between the two groups before and after therapy [18]. Moreover, the Pittsburgh sleep quality index (PSQI) was used to compare the sleep quality between the two groups before and after therapy [19].

Evaluation criteria of efficacy

According to Urticaria activity score over 7d (UAS7), the efficacy index was calculated [10]. Efficacy index = [(total UAS7 score before therapy - total UAS7 score after therapy) ÷ total UAS7 score before therapy] ×100%. Cured: the efficacy index was ≥90%. Effective: the efficacy index was ≥20% but <90%. Ineffective: the efficacy index was <20%. Total response rate = (1 - the number of ineffective cases/total cases) ×100%.

Table 1. Comparison of clinical data

Factor	Control group (n=35)	Observation group (n=40)	χ^2 value	*P* value
Age (years)	36.89±12.04	37.05±15.16	0.050	0.959
Sex			0.303	0.581
Male	11	15		
Female	24	25		
Course of disease (months)	12.53±7.65	13.09±11.70	0.091	0.927
BMI (kg/m^2)	24.54±3.24	25.33±3.84	0.955	0.342
History of hypertension			0.046	0.828
Yes	8	10		
No	27	30		
History of diabetes mellitus			0.321	0.570
Yes	6	5		
No	29	35		

Note: BMI: Body mass index.

Table 2. Evaluation of efficacy on patients

Group	Cured	Effective	Ineffective	Total response rate
Observation group (n=40)	22 (55.00%)	13 (32.50%)	5 (12.50%)	35 (87.50%)
Control group (n=35)	10 (28.57%)	14 (40.00%)	11 (31.43%)	24 (68.57%)
χ^2 value				3.985
P value				0.046

Statistical analyses

SPSS 25.0 software was used to analyze and process the collected data, and GraphPad Prism 8 software was used to visualize the processed data. The measurement data were expressed as mean ± standard deviation, and the independent sample t-test for was used for comparison between groups and paired t-test for that within groups. The counting data were expressed as rates and analyzed using chi-square test. P<0.05 indicates a statistical difference.

Results

Comparison of clinical data

According to comparisons, the two groups were not greatly different in age, sex, course of disease, body mass index, history of hypertension and diabetes mellitus (P>0.05, **Table 1**).

Evaluation of efficacy

Comparison of efficacy between the two groups revealed a significantly lower total response rate in the control group than that in the observation group (P<0.05, **Table 2**).

Comparison of serum immune indexes

According to comparison of IgE, IL-4 and IFN-γ levels between the two groups, the two groups were similar in the levels before therapy (P>0.05). After therapy, the levels of IgE and IL-4 in both groups decreased obviously, while the level of IFN-γ in both groups increased, with significantly lower levels of IgE and IL-4 and a significantly higher IFN-γ level in the observation group than those in the control group (P<0.05, **Figure 1**).

Changes of quality of life and pruritus degree

According to comparison of pruritus VAS scores and DLQI scores between the two groups, the two groups were not greatly different in the pruritus VAS and DLQI scores before therapy (P>0.05). After therapy, the pruritus VAS and DLQI scores in both groups decreased significantly, and the observation group had significantly lower pruritus VAS and DLQI scores than the control group (P<0.05, **Figure 2**).

Changes of anxiety and depression

According to comparison of anxiety and depression between the two groups, the two groups were not greatly different in HAMA and HAMD

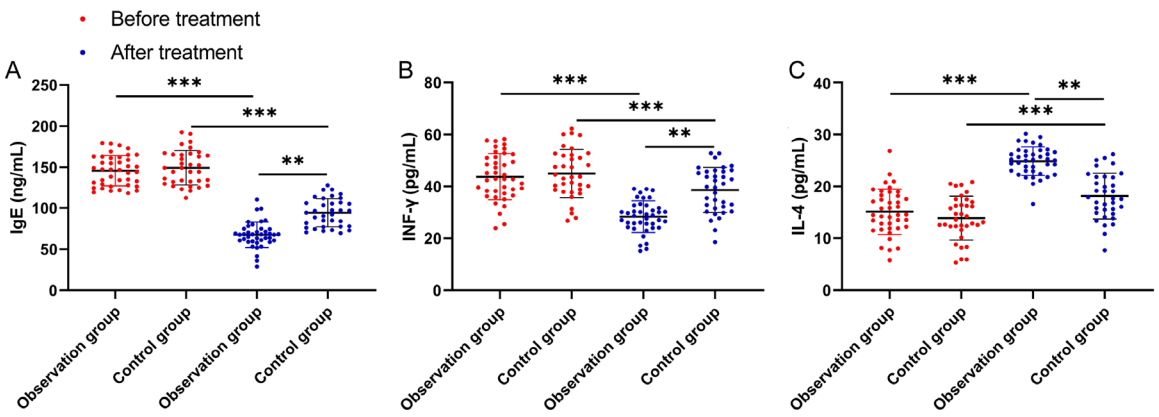

Figure 1. Expressions of IgE, IL-4 and IFN-γ in patients. A. Changes of IgE in patients before and after therapy; B. Changes of IFN-γ in patients before and after therapy; C. Changes of IL-4 in patients before and after therapy. Notes: Ig-E: Immunoglobulin E; IL-4: Interleukin-4; INF-γ: Interferon-γ. **P<0.01, ***P<0.001.

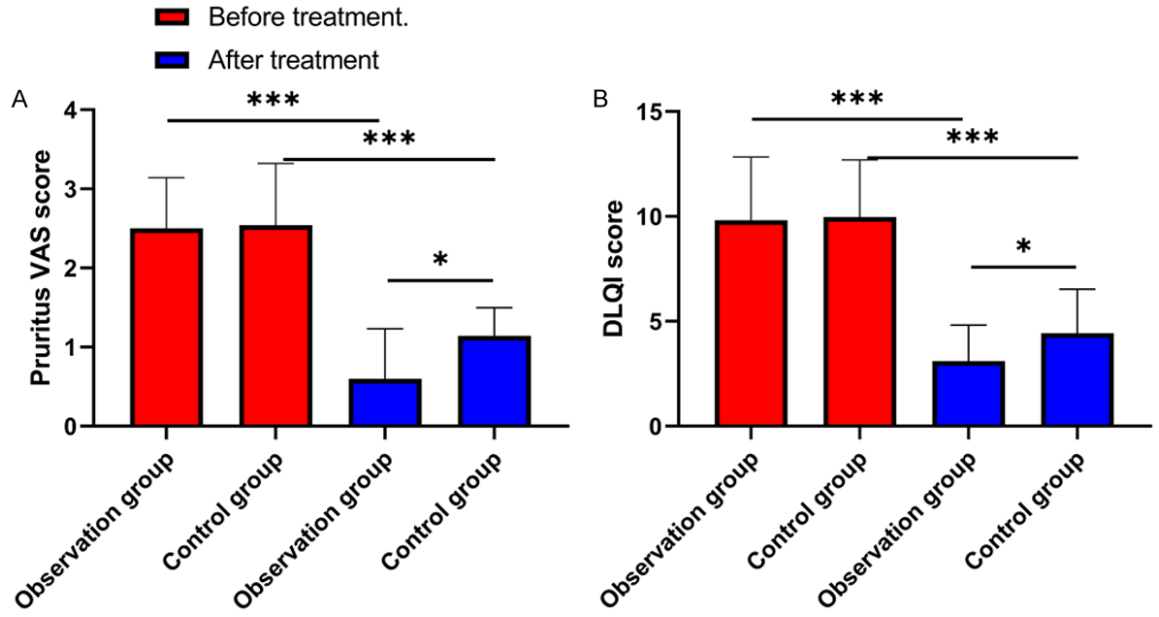

Figure 2. Comparison of quality of life and pruritus VAS score between the two groups. A. Changes of pruritus VAS scores in patients before and after therapy; B. Changes of DLQI scores in patients before and after therapy. Note: VAS: visual analogue scale; DLQI: Dermatology Quality of Life Index. *P<0.05, ***P<0.001.

scores before therapy (P>0.05). After therapy, HAMA and HAMD scores of both groups decreased significantly, and the observation group got lower HAMA and HAMD scores than the control group (P<0.05, **Figure 3**).

Changes of sleep quality

According to comparison of sleep quality between the two groups, the two groups were not greatly different in PSQI scores before therapy (P>0.05), while after therapy, PSQI scores of both groups decreased significantly, and the observation group had lower PSQI score than the control group (P<0.05, **Figure 4**).

Comparison of adverse reactions

Comparison of adverse reactions between the two groups revealed no notable difference in nausea, lethargy, ecchymosis and dizziness (P>0.05, **Table 3**), and the total incidence was also not significantly different between the two groups (P>0.05, **Table 3**).

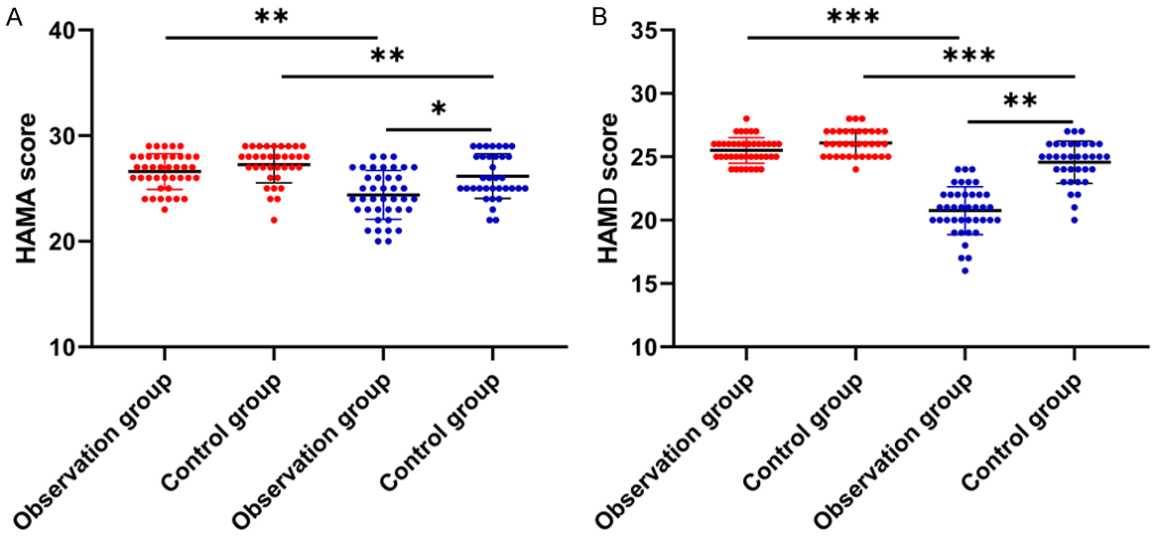

Figure 3. Comparison of anxiety and depression scores between the two groups. A. Changes of HAMA scores before and after therapy; B. Changes of HAMD scores before and after therapy. Note: HAMA: Hamilton anxiety rating scale; HAMD: Hamilton depression rating scale. *P<0.05, **P<0.01.

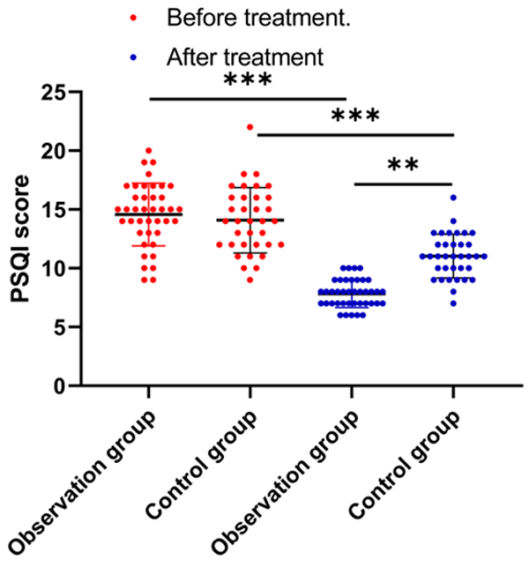

Figure 4. Changes of sleep quality score in patients. Note: PSQI: Pittsburgh sleep quality index. **P<0.01, ***P<0.001.

Discussion

CSU, as a kind of localized edema symptoms, is generally caused by the increased dilatation and permeability of small blood vessels in the skin and mucosa [20]. In clinical therapy, antihistamines, such as loratadine, cetirizine and ebastin, are often used in western medicine, and their dose is usually reduced after they take effect to maintain the effect at a minimum dose [21]. Drug therapy can temporarily relieve the symptoms of patients. However, due to the high recurrence rate of CSU, long course of disease and long-term drug treatment, patients will develop drug resistance, which leads to poor long-term treatment effect [22].

In TCM, CSU is classified into the category of rubella and urticaria, which belongs to deficiency in origin and excess in superficiality. It is considered that pathogenic wind is an important cause of the disease. Although the lesion is in the epidermis, the root of the disease is in the blood [23]. In this study, the effects of acupuncture combined with pricking and cupping therapy on CSU were compared with those of traditional therapy. According to the results, the observation group showed a significantly higher total response rate than the control group, and the pruritus VAS scores of both groups were improved. In addition, the two groups were not greatly different in adverse reactions. These results indicate that acupuncture combined with pricking and cupping therapy was more effective than the traditional treatment scheme and did not increase the occurrence of adverse reactions. Prior study by Ma et al [24] revealed that pricking and cupping therapy combined with Ebastine therapy was significantly more effective than Ebastine therapy for CSU patients. TCM believes that the treatment for CSU should focus on regulating Qi and blood, nourishing blood, promoting blood circu-

Table 3. Comparison of complications in patients

Group	Nausea	Lethargy	Ecchymosis	Dizziness	Overall incidence
Control group (n=35)	2 (5.71%)	3 (8.57%)	5 (14.28%)	4 (11.43%)	14 (40.00%)
Observation group (n=40)	3 (7.50%)	2 (5.00%)	2 (5.00%)	4 (10.00%)	11 (27.50%)
χ^2 value	0.095	0.095	1.902	0.039	1.313
P value	0.757	0.757	0.167	0.841	0.252

lation, softening liver, tonifying kidney, clearing heat, dispelling wind and relieving itching. Modern neuroanatomy has verified that there are corresponding spinal nerves and branches near each Jiaji acupoint [25]. Acupuncture at Jiaji acupoint in the distribution area of the corresponding ganglion segment of herpes can inhibit the pain nerve from transmitting pain information to the spinal cord and improve the pain valve of the body. Additionally, acupuncture at Jiaji acupoint can inhibit the response of spinal cord cells to nociceptive stimulation, reduce the transmission of pain impulse and the afferent impulse at the source of pain, and thus realize the Promote blood circulation and remove blood stasis, calm pain [26]. Bloodletting therapy can promote local blood circulation, alleviate inflammation and edema of local tissues, lower nerve stimulation and oppression, and promote nerve repair and regeneration [27]. The negative pressure of cupping causes congestion and edema of local tissues, and triggers various neuroendocrine reactions in nerves, muscles, blood vessels and subcutaneous glands. The warming effect of cupping can promote local blood circulation of skin lesions, enhance the permeability of blood vessel walls, and improve the tolerance of tissues to pain, thus effectively relieving pain [12]. The above is also the reason why acupuncture combined with pricking collaterals and cupping therapy is superior to traditional treatment.

In recent years, most scholars believe that the imbalance of the number and activity of two subtypes of helper T lymphocytes (Th1 and Th2) is the key factor to induce allergic diseases [28]. CSU is characterized by persistent pimple or wheals with severe itching, which is often caused by the degranulation of activated mast cells and the extravasation of dermis plasma [29]. Therefore, in this study, the changes of immune indexes in patients before and after therapy were also determined. IgE is a cytophilic reactive antibody that binds to Fc receptors on mast cells and basophils through the FCεRI segment [30]. When the body is exposed to the same allergen again, the allergen interacts with the IgE that binds to the cell surface [31]. IFN-γ and IL-4 are the characteristic cytokines of Th1 and Th2 cells, respectively. The functional status of Th1 and Th2 cells can be understood by detecting these two cytokines [32]. The results of this study revealed significantly lower levels of IgE and IL-4 and a significantly higher IFN-γ level in the observation group than those in the control group. The results indicate that acupuncture combined with pricking and cupping therapy can correct the imbalance of Th1 and Th2 in serum and reduce the content of IgE, the release of cellular transmitters and the permeability of blood vessels, so as to achieve a good effect on CSU. At the end of the study, the quality of life, negative emotion and sleep quality were compared between the two groups before and after therapy. It was found that the quality of life, sleep quality and negative emotion were improved more in the observation group after therapy. This is because acupuncture combined with pricking and cupping therapy can alleviate the symptoms of wheals and itching, relieve the anxiety and depression in CSU patients, and thus improve their sleep and quality of life.

This study has confirmed through analysis that acupuncture combined with pricking and cupping therapy can deliver higher efficacy in CSU patients. However, this study still has some limitations. First of all, the inclusion time is short, and the sample size is small, both of which may compromise the result analysis. Secondly, the patients were not followed up for a long time, so the effects of the two regimens on the recurrence of patients can't be understood. Finally, this is a single-center study, so more data are required for verification. Therefore, we hope to supplement clinical trials in follow-up research to improve the conclusions.

To sum up, acupuncture combined with pricking and cupping therapy is highly effective for

CSU because it can significantly alleviate symptoms and negative emotion, and improve the quality of life, sleep quality and the balance of Th1/Th2 cytokine in patients with CSU.

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Disclosure of conflict of interest

None.

Address correspondence to: Yanjun Wang, Department of Acupuncture and Moxibustion, The First Affiliated Hospital of Hebei College of Traditional Chinese Medicine, Shijiazhuang 050011, Hebei, China. E-mail: hbsjzwww@126.com

References

[1] Antia C, Baquerizo K, Korman A, Bernstein JA and Alikhan A. Urticaria: a comprehensive review: epidemiology, diagnosis, and work-up. J Am Acad Dermatol 2018; 79: 599-614.

[2] Maurer M, Fluhr JW and Khan DA. How to approach chronic inducible urticaria. J Allergy Clin Immunol Pract 2018; 6: 1119-1130.

[3] Maurer M, Khan DA, Elieh Ali Komi D and Kaplan AP. Biologics for the use in chronic spontaneous urticaria: when and which. J Allergy Clin Immunol Pract 2021; 9: 1067-1078.

[4] He L, Yi W, Huang X, Long H and Lu Q. Chronic urticaria: advances in understanding of the disease and clinical management. Clin Rev Allergy Immunol 2021; 61: 424-448.

[5] Johal KJ and Saini SS. Current and emerging treatments for chronic spontaneous urticaria. Ann Allergy Asthma Immunol 2020; 125: 380-387.

[6] Bracken SJ, Abraham S and MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. Front Immunol 2019; 10: 627.

[7] Kolkhir P, Altrichter S, Munoz M, Hawro T and Maurer M. New treatments for chronic urticaria. Ann Allergy Asthma Immunol 2020; 124: 2-12.

[8] Iriarte Sotes P, Armisen M, Usero-Barcena T, Rodriguez Fernandez A, Otero Rivas MM, Gonzalez MT, Meijide Calderon A and Veleiro B; Urtigal, the Galician Group of Interest in Urticaria. Efficacy and safety of up-dosing antihistamines in chronic spontaneous urticaria: a systematic review of the literature. J Investig Allergol Clin Immunol 2021; 31: 282-291.

[9] Miller RL, Shtessel M, Robinson LB and Banerji A. Advances in drug allergy, urticaria, angioedema, and anaphylaxis in 2018. J Allergy Clin Immunol 2019; 144: 381-392.

[10] Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang WH, Lim JJ, Clarke HJ, Galanter J, Chinn LW, Chu T, Teterina A, Burgess T, Haddon DJ, Lu TT and Maurer M. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nat Med 2021; 27: 1961-1969.

[11] Shi Y, Hou T, Zheng Q, Liu Y, Yang T and Li Y. Acupoint catgut embedding for patients with chronic urticaria: a systematic review protocol. Medicine (Baltimore) 2019; 98: e16036.

[12] Shi Y, Zhou S, Zheng Q, Huang Y, Hao P, Xu M, Zhang L, Xiao X, Zheng H and Li Y. Systematic reviews of pharmacological and nonpharmacological treatments for patients with chronic urticaria: an umbrella systematic review. Medicine (Baltimore) 2019; 98: e15711.

[13] Huang Z, Zhao N, Su Z, Su J and Wu Q. Effects of pricking and cupping combined with rehabilitation training on elbow flexion spasticity of upper limb after stroke and its IEMG value. Zhongguo Zhen Jiu 2018; 38: 119-125.

[14] Ye YJ, Xie YX, Yan TW, Liu SS, Wang B, Liu XR, Wang GT, Tang ZD, Ma W and Shen WD. Rolling needle pricking-cupping therapy and traditional pricking-cupping therapy for cervical spondylosis of neck type: a randomized controlled trial. Zhongguo Zhen Jiu 2020; 40: 1299-1303.

[15] Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, Ballmer-Weber B, Bangert C, Ben-Shoshan M, Bernstein JA, Bindslev-Jensen C, Brockow K, Brzoza Z, Chong Neto HJ, Church MK, Criado PR, Danilycheva IV, Dressler C, Ensina LF, Fonacier L, Gaskins M, Gaspar K, Gelincik A, Gimenez-Arnau A, Godse K, Goncalo M, Grattan C, Grosber M, Hamelmann E, Hebert J, Hide M, Kaplan A, Kapp A, Kessel A, Kocaturk E, Kulthanan K, Larenas-Linnemann D, Lauerma A, Leslie TA, Magerl M, Makris M, Meshkova RY, Metz M, Micallef D, Mortz CG, Nast A, Oude-Elberink H, Pawankar R, Pigatto PD, Ratti Sisa H, Rojo Gutierrez MI, Saini SS, Schmid-Grendelmeier P, Sekerel BE, Siebenhaar F, Siiskonen H, Soria A, Staubach-Renz P, Stingeni L, Sussman G, Szegedi A, Thomsen SF, Vadasz Z, Vestergaard C, Wedi B, Zhao Z and Maurer M. The international EAACI/GA (2) LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022; 77: 734-766.

[16] Choi GS, Nam YH, Park CS, Kim MY, Jo EJ, Park HK and Kim HK. Anxiety, depression, and

stress in Korean patients with chronic urticaria. Korean J Intern Med 2020; 35: 1507-1516.
[17] Rencz F, Gergely LH, Wikonkal N, Gaspar K, Pentek M, Gulacsi L, Tamasi B, Poor AK, Kinyo A, Bali G, Hidvegi B, Sardy M, Hajdu K, Szegedi A, Remenyik E, Bata-Csorgo Z, Hollo P, Baji P and Brodszky V. Dermatology life quality index (DLQI) score bands are applicable to DLQI-relevant (DLQI-R) scoring. J Eur Acad Dermatol Venereol 2020; 34: e484-e486.
[18] Liu Z, Qiao D, Xu Y, Zhao W, Yang Y, Wen D, Li X, Nie X, Dong Y, Tang S, Jiang Y, Wang Y, Zhao J and Xu Y. The efficacy of computerized cognitive behavioral therapy for depressive and anxiety symptoms in patients with COVID-19: randomized controlled trial. J Med Internet Res 2021; 23: e26883.
[19] Farah NM, Saw Yee T and Mohd Rasdi HF. Self-reported sleep quality using the malay version of the pittsburgh sleep quality index (PSQI-M) in Malaysian adults. Int J Environ Res Public Health 2019; 16: 4750.
[20] Gimenez-Arnau AM, DeMontojoye L, Asero R, Cugno M, Kulthanan K, Yanase Y, Hide M and Kaplan AP. The pathogenesis of chronic spontaneous urticaria: the role of infiltrating cells. J Allergy Clin Immunol Pract 2021; 9: 2195-2208.
[21] Goncalo M, Gimenez-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein JA, Ensina LF, Fomina D, Galvan CA, Godse K, Grattan C, Hide M, Katelaris CH, Khoshkhui M, Kocaturk E, Kulthanan K, Medina I, Nasr I, Peter J, Staubach P, Wang L, Weller K and Maurer M. The global burden of chronic urticaria for the patient and society. Br J Dermatol 2021; 184: 226-236.
[22] Nochaiwong S, Chuamanochan M, Ruengorn C, Awiphan R, Tovanabutra N and Chiewchanvit S. Evaluation of pharmacologic treatments for H1 antihistamine-refractory chronic spontaneous urticaria: a systematic review and network meta-analysis. JAMA Dermatol 2021; 157: 1316-1327.
[23] Wang YM, Du L and Zhu YJ. Evidence-based therapies of Chinese medicine for chronic urticaria: where do we stand and where are we going? Chin J Integr Med 2017; 23: 566-569.
[24] Ma B, Chen X, Liang Y, Ouyang W, Tang B, Meng F, Quan X, Wang C, Li Y and Chen D. Efficacy of bloodletting therapy in patients with chronic idiopathic urticaria: a randomized control trial. Evid Based Complement Alternat Med 2020; 2020: 6598708.
[25] Shen S, Wang M and Dong J. Moxibustion therapy for chronic spontaneous urticaria: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2020; 99: e23226.
[26] Shi Y, Zheng H, Zhou S, Zheng Q, Zhang L, Xiao X, Cao W, Liu Y and Li Y. Efficacy and safety of acupuncture for patients with chronic urticaria: study protocol of a randomized, sham-controlled pilot trial. Trials 2019; 20: 326.
[27] Huo HM. Efficacy observation on acupuncture combined with bloodletting for chronic urticarial. Zhongguo Zhen Jiu 2014; 34: 41-43.
[28] Chen Q, Zhong H, Chen WC, Zhai Z, Zhou Z, Song Z and Hao F. Different expression patterns of plasma Th1-, Th2-, Th17- and Th22-related cytokines correlate with serum autoreactivity and allergen sensitivity in chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 2018; 32: 441-448.
[29] Maheshwari A, Garg T, Chander R and Debnath E. Chronic spontaneous urticaria: an etiopathogenic study. Indian J Dermatol 2022; 67: 92.
[30] Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, Scheffel J, Siebenhaar F, Steinert C, Terhorst-Molawi D, Xiang YK, Church MK and Maurer M. Total IgE as a marker for chronic spontaneous urticaria. Allergy Asthma Immunol Res 2021; 13: 206-218.
[31] Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, Shulzhenko A, Fomina D and Maurer M. Autoimmune chronic spontaneous urticaria detection with IgG Anti-TPO and total IgE. J Allergy Clin Immunol Pract 2021; 9: 4138-4146, e4138.
[32] Xu D, Li Z and Wang Y. Efficacy of fangfeng tongsheng granule combined with levocetirizine in the treatment of chronic urticaria and its effect on serum complement, IL-4, IgE, and IFN-gamma levels in patients. Evid Based Complement Alternat Med 2022; 2022: 4012416.