



Short communication

Retrospective case series on *Gwakhyangjeonggi-san* prescribed to patients with chronic urticaria

Ji-Hwan Kim, Seong-Sik Park*

Department of Sasang Constitutional Medicine, Dongguk University Bundang Hospital, 87-2 Sunae3-dong, Bundang-gu, Seoungnam-si, Gyeonggi-do 463-865, Republic of Korea

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ABSTRACT

Introduction: Chronic urticaria (CU) is characterized by repeated occurrence of wheals or itching for more than 6 weeks. When urticarial symptoms repeatedly occur despite taking western medicines such as antihistamines, herbal medicines have potential as an alternative for them. Among various herbal medications for CU, we mostly prescribe *Gwakhyangjeonggi-san* (GJS) made by Lee Je-ma, the founder of Sasang Constitutional Medicine (SCM) in Korea. The purpose of this study is to investigate whether GJS actually helps in treating CU.

Methods: We performed a retrospective review of the medical records of 30 patients to whom GJS was administered in order to compare the changes in urticaria activity scores (UAS) and in western medicines taken at the beginning of treatment of GJS and at 6 months after completion of the treatment.

Results: The UAS after 6 months from treatment (1.63 ± 2.06) with GJS for an average of 57.30 ± 35.88 days was significantly decreased compared to the score before treatment (5.10 ± 0.99), showing a statistically significant difference ($p < 0.001$). 46.67% of the patients (14/30 patients) reported that their symptoms were completely eliminated, and 66.67% of the patients taking anti-histamines (18/27 patients) were able to stop it completely.

Discussion: Based on the findings, GJS helps patients reduce taking western medicines such as anti-histamines, and we hypothesize that GJS improves symptoms of CU by the gastrointestinal protective activity and anti-oxidative/depressive effect. Further clinical study is warranted.

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1. Introduction

Chronic urticaria (CU)¹ is characterized by repeated occurrence of wheals or itching for more than 6 weeks, and etiological causes are not clear. The treatment of CU involves alleviation of symptoms by prescribing antihistamines until the disease is healed naturally.^{2,3} Various medicines such as corticosteroids or cyclosporine may be required with poor response to antihistamines, but potential adverse effects of them limit therapeutic regimens.^{4–6} Patients suffering recurring symptoms despite the repeated administration of western medicines are likely to seek treatment methods to substitute for them. In East Asian regions, by virtue of safety and fewer side effects, a variety of herbal medicines such as *Xiao-Feng San* are used in the treatment of CU,^{7–9} and they are likely to be a good substitute for western medicines. We are also prescribing a variety of herbal medicines to CU patients in our

outpatient clinic, and among them, the most-prescribing decoction is *Gwakhyangjeonggi-san* (GJS)¹⁰ made by Lee Je-ma, the founder of Sasang Constitutional Medicine (SCM) in Korea. However, we can hardly find clinical reports about GJS for CU. In this study, we investigate that GJS actually helps in treating CU.

2. Methods

We consecutively chose and retrospectively reviewed medical records of 30 CU patients (Table 1) who visited Dongguk University Bundang Hospital from December 2012 to June 2013, and were treated with GJS for at least one month. Prior consents were obtained.

GJS was prepared as follows. The amount twice the dose of herbs (Table 2) was boiled in 700 ml distilled water for 2 h to concentrate it to 240 ml. Then, GJS was administered to patients twice a day, 30 min after meals in the morning and evening. For children under the age of 10, 1/3 of the amount for adults was administered. The treatment periods of each patient depended on the intensity of symptoms.

* Corresponding author. Tel.: +82 31 710 3723; Fax: +82 31 710 3780.
E-mail address: parkss@dongguk.ac.kr (S.-S. Park).

Table 1Patients' characteristic, and changes in both symptoms of urticaria and western medicines taken before and 6 months after treatment with *Gwakhyangjeonggi-san* (GJS).

	Sex/Age	BMI (kg/m ²)	Disease duration (Months)	Treatment duration (Days)	Wheals or hives (A)		Itch (B)		Urticaria activity score (A + B)		Anti-histamines (with steroids or sedatives)	
					Pre ^a	F/U ^b	Pre	F/U	Pre	F/U	Pre	F/U
1	F/42	19.25	2	49	1	1	3	1	4	2	○ ^c	△ ^d
2	F/31	20.87	2	20	2	1	1	1	3	2	○	△
3	F/31	20.94	2	56	3	0	3	0	6	0	○ (Steroids)	
4	F/33	19.96	3	22	3	1	3	0	6	1	○	△
5	F/20	17.08	3	30	3	0	3	0	6	0	○	
6	M/13	18.36	3	79	2	2	3	3	5	5		
7	F/27	27.03	3	57	3	0	3	0	6	0	○	
8	F/30	20.25	3	62	3	0	3	0	6	0	○	
9	F/24	22.24	3	27	3	0	3	0	6	0	○	
10	F/21	19.74	4	32	2	1	1	1	3	2		
11	F/29	19.74	4	120	3	0	3	0	6	0	○ (Steroids)	
12	F/31	21.98	4	49	2	1	1	0	3	1	○	
13	F/30	17.09	4	35	3	0	3	2	6	2	○	
14	M/9	16.07	4	44	2	0	3	0	5	0	○ (Sedatives)	
15	F/39	19.81	6	148	3	3	3	3	6	6	○	○
16	F/27	21.03	7	25	3	0	3	0	6	0	○	
17	F/6	17.25	11	46	2	0	3	0	4	0	○ (Sedatives)	
18	F/46	23.17	11	39	2	2	3	3	5	5		
19	M/23	24.08	14	100	1	0	3	0	4	0	○	
20	F/29	19.68	16	51	2	0	3	1	5	1	○	
21	F/54	19.43	16	71	2	0	3	0	5	0	○	
22	F/31	18.25	17	43	1	0	3	0	4	0	○	
23	F/26	18.25	19	141	2	1	3	1	5	2	○	
24	M/23	20.6	22	35	3	0	3	0	6	0	○	
25	F/17	18.19	32	86	2	1	3	1	5	2	○	○
26	F/30	19.93	36	44	3	0	3	0	6	0	○	
27	F/40	19.93	40	29	2	1	3	1	5	2	○ (Steroids)	○
28	M/9	16.41	48	19	3	3	3	3	6	6	○	○
29	F/23	19.12	60	39	2	2	3	3	5	5	○	○
30	F/50	21.19	97	121	2	2	3	3	5	5	○	○
Total 30 persons									14 ^e	27 ^f	9 ^g (18 ^h)	
Male:female 5:25		19.90	16.53	57.30	2.33	0.73	2.80	0.90	5.10	1.63	46.67% (14 ^e /30)	
Age 28.13 ± 11.42		±2.32	±21.45	±35.88	±0.66	±0.94	±0.61	±1.18	±0.99	±2.06	66.67% (18 ^h /27 ^f)	
(Mean ± Standard-deviation)												

^a Pre, Pre-treatment.^b F/U, Follow-up after 6 months from the last treatment.^c ○, Regularly taking anti-histamines.^d △, Taking anti-histamines whenever necessary^e 14, Fourteen persons whose symptoms disappeared 6 months after the last treatment.^f 27, Twenty-seven persons who already took western medicines before treatment.^g 9, Nine persons who still took western medicines 6 months after the last treatment.^h 18, Eighteen persons who stopped western medicines 6 months after the last treatment.

Table 2
Compositions and dose of one-time of *Gwakhyangjeonggi-san* (GJS) in Sasang Constitutional Medicine (SCM) and *Huoxiang-zhengqi-san* (HZS) in Traditional Chinese Medicine (TCM).

Medicinal plants	Scientific name	Weight (g)	
		GJS in SCM ^a	HZS in TCM ^b
<i>Agastachis Herba</i>	<i>Agastache rugosa</i> Fischer et Meyer O. Kuntze	6	6
<i>Perillae Folium</i>	<i>Perilla frutescens</i> var. <i>acuta</i> Kudo	4	4
<i>Pinelliae Tuber</i>	<i>Pinellia ternata</i> Breitenbach	2	2
<i>Arecae Pericarpium</i>	<i>Areca Catechu</i> Linne	2	2
<i>Glycyrrhizae Radix</i> <i>Preparta cum Mel</i>	<i>Glycyrrhiza uralensis</i> Fischer, <i>Glycyrrhiza glabra</i> Linne	2	2
<i>Citri Unshius Pericarpium</i>	<i>Citrus unshiu</i> Markovich	2	2
<i>Citri Unshius Pericarpium</i> <i>Immaturus</i>	<i>Citrus unshiu</i> Markovich	2	
<i>Atractylodis Rhizoma</i>	<i>Atractylodes chinensis</i> Koidzumi	2	
<i>Atractylodis Rhizoma Alba</i>	<i>Atractylodes macrocephala</i> Koidzumi	2	2
<i>Cinnamomi Cortex</i>	<i>Cinnamomum cassia</i> Blume	2	
<i>Zizyphi Fructus</i>	<i>Zizyphus jujuba</i> Miller var. <i>inermis</i> Rehder	2	
<i>Alpiniae Oxyphyllae Fructus</i>	<i>Alpinia oxyphylla</i> Miquel	2	
<i>Zingiberis Rhizoma</i>	<i>Zingiber officinale</i> Roscoe	2	
<i>Zingiberis Rhizoma Recens</i>	<i>Zingiber officinale</i> Roscoe	2	
<i>Angelicae Dahuricae Radix</i>	<i>Angelica dahurica</i> Benthham et Hooker		2
<i>Poria Sclerotium</i>	<i>Poria cocos</i> Wolf		2
<i>Magnoliae Cortex</i>	<i>Magnolia officinalis</i> Rehder et Wilson		2
<i>Platycodonis Radix</i>	<i>Platycodon grandiflorum</i> A. De Candolle		2
Total amounts		34	28

^a GJS in SCM: *Gwakhyangjeonggi-san* in Sasang Constitutional Medicine.

^b HZS in TCM: *Huoxiang-zhengqi-san* in Traditional Chinese Medicine.

We compared the urticaria activity score (UAS; Total scores 0~6)^{11,12} which patients rated by themselves before treatment and after 6 months from the last treatment. CU has a high probability of recurrence, and in order to verify the effect of GJS on CU, we measured UAS after 6 months from the last treatment instead of the treatment completion. Also, types of western medicines were compared before and after 6 months with GJS.

All data were analyzed using Window SPSS 20.0, and the changes of UAS were analyzed by Wilcoxon signed rank test. P-values less than 0.05 were considered statistically significant. All data were expressed in mean $\pm$ SD.

3. Results

Thirty patients (Male:Female 5:25; Mean age 28.13 ± 11.42 years; mean body mass index 19.90 ± 2.32 kg/m²) had been suffering CU for an average of 16.53 ± 21.45 months, and were treated with GJS for 57.30 ± 35.88 days. The average scores for wheals, itching, and UAS before treatment were 2.33 ± 0.66 , 2.80 ± 0.61 , and 5.10 ± 0.99 , respectively, but they were reduced to 0.73 ± 0.94 , 0.90 ± 1.18 , and 1.63 ± 2.06 after 6 months. These changes were also statistically significant ($p < 0.001$) (Table 1, and Fig. 1). In particular, the symptoms of 14 out of 30 patients (46.67%) were completely eliminated (UAS = 0). On the other hand, 27 out of 30 patients had been taking anti-histamines even before treatment with GJS, but after 6 months from the last treatment with GJS, 18 (66.67%; 18/27) patients were able to stop the administration of anti-histamines. Four out of 5 patients (Patient number; P# 3, 11, 14, and 17 in Table 1) who had been taking steroids or sedatives along with anti-histamines due to severe symptoms were able to stop taking them after treatment with GJS. Three patients (P# 1, 2, and 4) who had been taking anti-histamines regularly were able to reduce the number of times of taking the drugs. However, 6 patients (P# 6, 15, 18, 28, 29, and 30) showed no significant changes of UAS before and after treatment with GJS.

4. Discussion

GJS in SCM is derived from *Huoxiang-zhengqi-san* in Traditional Chinese Medicine (Table 2).¹³ Lee Je-ma in his book, *Dong-Yi-Soo-Se-Bo-Won* (*The Principle of Life Preservation in Oriental medicine*)¹⁴

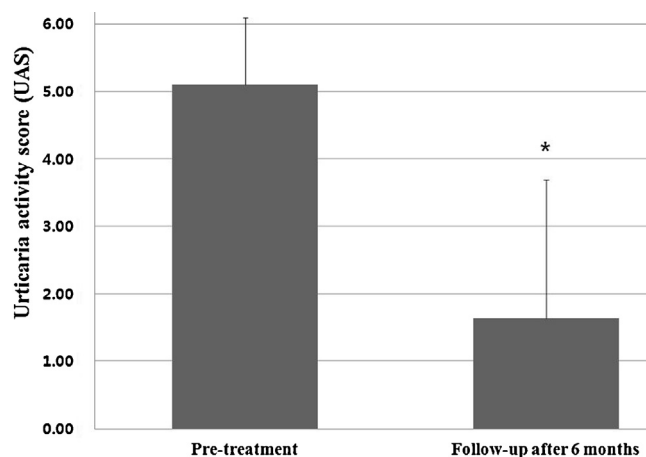


Fig. 1. Urticaria activity scores (UAS) before and 6 months after *Gwakhyangjeonggi-san* (GJS) treatment in Sasang Constitutional Medicine for chronic urticaria (CU). UAS, which ranges from 0 (none) to 6 (Severe), includes scores for both wheal or hives and itch, of which each topic is up to 3 points. Six months after treatment with GJS for CU, UAS (1.63 ± 2.06) was much lower than before treatment (5.10 ± 0.99). The result was statistically significant (Wilcoxon signed rank test: * $p < 0.001$).

often used GJS for people who do not have good appetite and often suffer gastrointestinal disorders such as irritable bowel syndrome physically,^{15,16} or tend to be nervous psychologically.¹⁷

Recent experimental studies in Korea have reported that GJS is effective on anti-allergic effect.^{10,13} *Agastachis Herba*, the main ingredient of GJS has been used for treatment of anorexia, vomiting, and diarrhea, however, some experimental studies examined that *Agastachis Herba* had an anti-fungal¹⁸ and anti-oxidative¹⁹ effect. *Cinnamomi Cortex* has both anti-oxidative effects²⁰ and gastroprotective activities²¹ during regular ingestion. Other components of GJS such as *Citri Unshius Pericarpium*²² and *Alpiniae Oxyphyllae Fructus*²³ also have anti-oxidative effect due to various mechanisms. Type I hypersensitivity reactions are commonly implicated in cutaneous adverse food reactions.²⁴ Gluten which causes gastrointestinal symptoms such as celiac disease, and pseudo-allergens such as aromatic compounds or artificial preservatives may be associated with the occurrence of CU.²⁵ Oxidative stress conditions were observed in the skin lesions of patients with

idiopathic CU.^{26–28} Therefore, it seems that *Agastachis Herba* and *Cinnamomi Cortex* can help preventing repeated adverse food reactions from deteriorating into CU, and herbs with anti-oxidative effects in GJS work synergistically to contribute to decreasing the symptoms of CU.

Perillae Folium, the second main ingredient in GJS has an anti-depressive effect.²⁹ CU patients often suffer lack of sleep due to chronic itching or have difficulty in personal relationships and social activities due to external urticarial lesion or angioedema.³⁰ Therefore, it is inferred that *Perillae Folium* helps reduce the mental stress instead of sedatives, which occurs as quality of life deteriorates due to CU.

As a result, GJS has potential as an alternative for long-term users of western medicines who suffer refractory CU with lack of sleep, mental irritability, and physical discomfort such as gastrointestinal disorders.

Our case series, by the nature of retrospective study, have no control allowing various biases and errors. GJS has not yet received 'Good Manufacturing Practice'. Despite these limitations, further studies on GJS will make a contribution to investigate its efficacy.

Conflict of interests

The authors declare no conflicts of interests.

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