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Original Article

Impact of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) on Treatment of Chronic Spontaneous Urticaria: A Randomized Controlled Study

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ABSTRACT **Objective:** To study the effect of Jumihaidokuto (Shi-Wei-Bai-Du-Tang, 十味敗毒汤) in the management of chronic spontaneous urticaria. **Methods:** A randomized two-arm, parallel group study was conducted to compare the effect of Jumihaidokuto (6 g daily) with a control for 8 weeks. Concomitant therapy (e.g., antihistamines) was continued. Twenty-one subjects with severe chronic urticaria were enrolled in this study. The primary treatment outcome was the severity score proposed by the Japanese Dermatological Association. Secondary outcomes were quality of life (Skindex-16), itch intensity (Visual Analogue Scale), and patients' subjective disability due to wheal or itch. After the subjects were randomly assigned to groups by block randomization, 10 received Jumihaidokuto, and 11 did not. All subjects had already taken antihistamines. **Results:** Improvement was significant when comparing the severity score of the Jumihaidokuto group with that of the control group ($P<0.01$). Skindex-16 values for both groups gradually decreased in the same fashion. **Conclusion:** Concomitant use of Jumihaidokuto with antihistamine was more effective than antihistamine alone in the management of chronic idiopathic urticaria. (Trial Registration No. UMIN000007251)

KEYWORDS Jumihaidokuto, crude drug extract, Shi-Wei-Bai-Du-Tang, Chinese medicine, antihistamine, chronic spontaneous urticaria, severity, quality of life

Chronic spontaneous urticaria (CSU) is a common skin disease characterized by the spontaneous development of wheals with pruritus that persist for more than 4 weeks.[1] The symptoms related to CSU significantly impair one's quality of life (QOL) and work productivity.[2-4] In the management of CSU, antihistamines are recommended as a first-line treatment and yield satisfactory therapeutic efficacy.[1,5,6] If their effects are insufficient, higher doses of antihistamines, leukotriene antagonists, and H_2-blockers will be applied. If these fail to resolve the symptoms, an alternative therapy is immunosuppressive drugs. To address the pathological mechanism in CSU, antihistamines play a central role in treatment. Alternative therapies may be prescribed to improve urticarial diathesis (e.g., atopic predisposition, autoimmunity, and bacterial infection).[7,8] However, despite uncertainty regarding the efficacy of combination treatment, these alternative therapies are generally used concomitantly with antihistamines. Although these treatment options can temporarily suppress symptoms related to CSU, wheals are easily reactivated by psychological stress, physical exhaustion, or infectious diseases.[1] Prolonged treatment with medications is required for the management of CSU. A safe and effective treatment, which can be administered for long periods of time, should be chosen. A previous study reported the beneficial therapeutic effect of combining antihistamine with total glucosides of paeony in the treatment of chronic urticaria.[9] This result suggests that herbal ingredients may be useful as effective therapeutic options for the treatment of CSU.

Jumihaidokuto (Shi-Wei-Bai-Du-Tang, 十味敗毒汤) is an extract powder comprised of a mixture of crude drug extracts and is covered by Japanese insurance for the treatment of the following symptoms: suppurative dermatosis, acute dermatitis, urticaria, acute eczema, and tinea pedis. Regarding

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the pharmacological properties of Jumihaidokuto, 5-alpha-reductase inhibition, antioxidant activity, and enhancement of type-1 macrophage function are considered the major mechanisms by which dermatitis is suppressed.[10-12] A prospective uncontrolled case series evaluated the efficacy of concomitant treatment with Jumihaidokuto on the dermatological symptoms of atopic dermatitis. The results showed that 12 weeks of treatment significantly decreased the eruption score (especially for erythema and acute papules), oozing and crusting, chronic papules, nodular lichenification, and eruption area.[13] To our knowledge, there are currently few studies that have evaluated its clinical efficacy for treating CSU. Thus, in this study, we evaluated the effects of concomitant use of Jumihaidokuto with antihistamine on CSU in a randomized controlled study.

METHODS

Diagnostic, Inclusion and Exclusion Criteria

This study was approved by the Institutional Ethics Committee (institutional ID 10303-2) and performed at Osaka University Hospital, Japan. Subjects who satisfied both the definition of urticaria[1] and the following conditions at the initiation of this study were included. Patients had infesting urticaria for more than 1 month, were treated with oral antihistamine for more than 1 month, had a severity score of more than 3 points when assessed by the management guidelines set by the Japanese Dermatology Association,[1] were at least 15 years old, and provided written consent. Subjects were excluded from the study if they had any of the following conditions: exhaustion, severe constipation, concomitantly taking other herbal medicines or oral corticosteroids in the 4 weeks prior to enrollment, and complications (e.g., aldosterone, myopathy, hypocalcemia, renal failure, heart failure, and pregnancy).

Grouping and Treatment

Subjects were randomly assigned to treatment groups with or without Jumihaidokuto by block randomization using random allocation software. The allocation table was concealed by the person who created the table and was responsible for allocation; this person was not involved in the treatment. A total of 50 subjects were expected to recruit, and this sample size was based on a previous study that had compared the effect of ketotifen with and without herbal medicines on chronic urticaria.[14] The recruitment period was January 16, 2012 to March 31, 2014, and the end of follow-up was April 30, 2014. Finally, 21 subjects were enrolled in this study (allocation ratio of Jumihaidokuto-treated group: antihistamine-only group=10:11). Recruitment was halted before we enrolled the expected number of subjects because of the study period stated in the experimental design approved by the ethics committee. Subjects in the Jumihaidokuto treatment group were asked to take 3 g Jumihaidokuto (Kracie Pharma Ltd., Japan, Table 1) just before breakfast and dinner, in addition to the concomitant antihistamines for 8 weeks. During the study period, changes in the medication regimen, such as altering dosage or taking additional medication (including topical drug), were prohibited. The trial registry ID is UMIN000007251.

Table 1. Components of Jumihaidokuto

Herb	Content (g)
Bupleuri radix	2.5
Platycodi radix	2.5
Cnidii rhizoma	2.5
Poria	2.5
Saposhnikoviae radix	2.5
Glycyrrhizae radix	1.5
Zingiberis rhizoma	1.0
Schizonepetae Spica	1.5
Araliae cordatae rhizoma	1.5
Pruni Cortex	2.5

Notes: Each daily dose (6.0 g) of this product contains 3,900 mg of Jumihaidokuto extract powder extracted from the mixture of the above crude drugs

Evaluation of Treatment Effect

Clinical evaluations were performed at weeks 0, 4, and 8. The primary endpoint of this study was the severity score for urticaria proposed by the Japanese Dermatology Association (1: symptom is not recognized, 2: mild symptoms, 3: tolerable but uncomfortable, 4: difficult to manage life with the symptoms, 5: cannot manage a social life, 6: shock or similar to shock).[1] Secondary endpoints were the Skindex-16, visual analogue scale (VAS) for itch (0 cm: no itch, 10 cm: worst itch), a patient questionnaire about itch and their skin condition (Appendix 1), and adverse events due to treatment. No changes were made to trial outcomes after the trial commenced.

Statistical Analysis

Data were expressed as mean ± standard

deviation ($\bar{x} \pm s$). The Bonferroni and Steel-Dwass multiple comparison tests were performed using Startle® version 3. Statistical analyses using Mann-Whitney U-test and Wilcoxon test were performed using StatView® for Windows ver. 4.54. *P* value less than 0.05 were considered statistical significant.

RESULTS

Demographic Background of Study Subjects

Twenty-one subjects with intractable chronic urticaria [male:female=11:10, age 39.0 ± 12.7 years (range: 20–65 years) with disease lasting 13.6 ± 8.9 months (range 3–36 months)] were enrolled in this study. During the study period, no subjects dropped out or declined to participate in the study protocol, and no adverse events or side effects occurred. Ten subjects were assigned to the group that received Jumihaidokuto, and 11 were assigned to the group that did not receive Jumihaidokuto (Figure 1). Demographic characteristics of the Jumihaidokuto-treated group were as follows: male:female = 7:3, age 38.8 ± 14.4 years, and disease duration 15.5 ± 8.9 months. The demographic characteristics of the group that did not receive Jumihaidokuto were: male:female = 4:7, age 39.2 ± 11.4 years, and disease duration 11.9 ± 9.0 months.

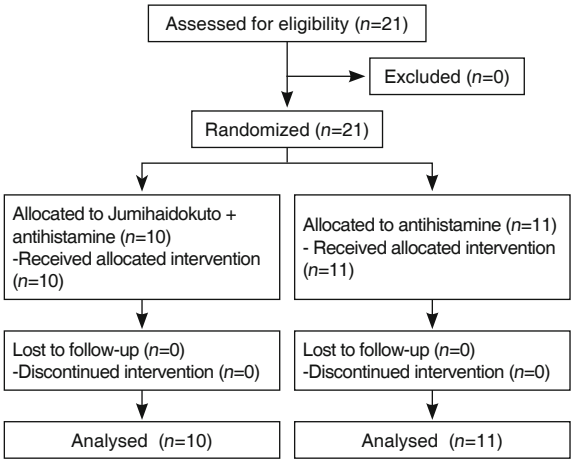

Figure 1. Flow Diagram of Jumihaidokuto Treatment for Chronic Spontaneous Urticaria

Impact of Jumihaidokuto on Disease Severity

At baseline, there were no apparent differences between the two treatment groups. When comparing the disease severity at 0 and 8 weeks, both groups showed statistically significant improvement ($P<0.05$). Disease severity for the antihistamine + Jumihaidokuto group at 8 weeks was significantly lower than that of the antihistamine only group ($P<0.05$). The change in the severity score was significantly larger for the antihistamine + Jumihaidokuto group compared with the antihistamine only group ($P<0.01$, Figure 2).

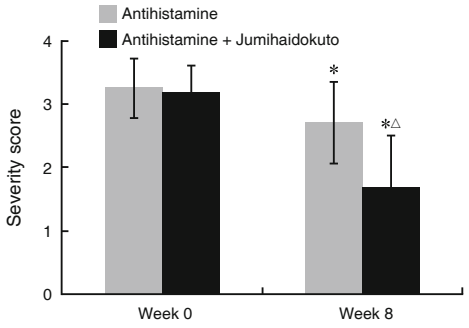

Figure 2. Comparison of Disease Severity at Week 0 and 8 between Groups

Notes: *$P<0.05$ *vs.* week 0 by Wilcoxon test; △$P<0.01$ *vs.* antihistamine group at 8 weeks by Mann-Whitney U test

Impact of Jumihaidokuto on Subjective Assessment

Itch VAS tended to decrease 8 weeks after the initiation of this study in both the antihistamine only and antihistamine + Jumihaidokuto treatment groups; however, these decreases were not statistically significant between groups ($P>0.05$). Relative change in the itch VAS score was not significantly different between the two groups (Figure 3A). Results from the brief questionnaire about the frequency of itch or visible symptoms (e.g., wheal and erythema) showed the superiority of Jumihaidokuto treatment for both itch and symptoms ($P<0.05$, Figure 3B).

Impact of Jumihaidokuto on QOL

The Skindex-16 total score tended to decrease after 8 weeks of treatment in both the antihistamine and antihistamine + Jumihaidokuto groups, but this difference was not statistically significant (Figure 4A). To further evaluate these results, we divided the Skindex-16 questions into different core domains (e.g., symptom, emotion, and functioning) and compared the differences between 0 and 8 weeks for each domain (Figure 4B). Differences in both the symptom and emotion domains were larger for the antihistamine + Jumihaidokuto group. Concerning the statistical analysis, although parametric analysis using Bonferroni's multiple comparison test found statistical significance regarding the efficacy of Jumihaidokuto ($P<0.05$), non-parametric analysis using the Steel-Dwass multiple comparison test did not detect a significant difference between the two groups.

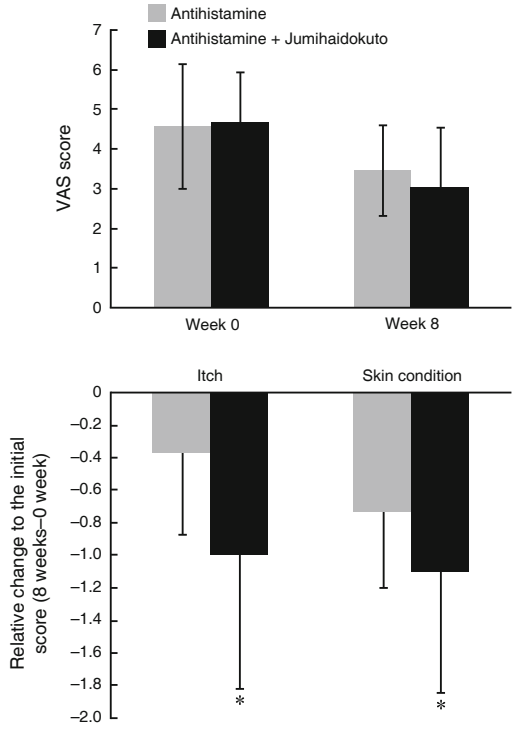

Figure 3. Comparison of Itch VAS Score and Brief Questionnaire Score between Groups ($\bar{x} \pm s$)

Note: *P<0.05 *vs*. antihistamine group by Steel-Dwass multiple comparison test

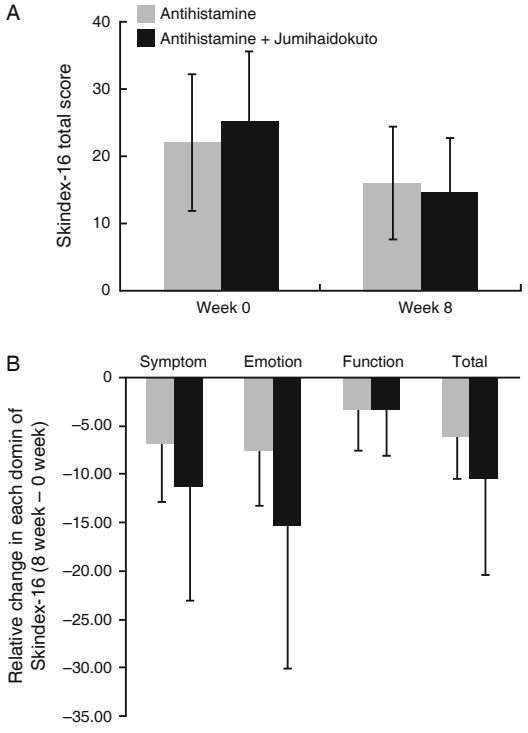

Figure 4. Comparison of Total and Relative Change in Each Domin of Skindex-16 between Groups

Adverse Events

During the study period, adverse event was not found in all study subjects.

DISCUSSION

In this study, we found that Jumihaidokuto was therapeutic for the treatment of CSU. The concomitant use of Jumihaidokuto with antihistamine for 8 weeks effectively decreased the disease severity score when compared with antihistamine alone. However, we did not find a significant difference between the Skindex-16 total scores of the Jumihaidokuto + antihistamine and antihistamine only groups using non-parametric statistical analysis (Steel-Dwass multiple comparison test, Appendix 2). These results suggest that the addition of Jumihaidokuto may attenuate the frequency of bouts of spontaneous urticaria. We speculate that the incomplete remission of CSU at 8 weeks might not be fully appreciated by comparing the Skindex-16 total scores; however, parametric statistical analysis (Bonferroni's multiple comparison test) of the Skindex-16 scores showed statistically significant improvement for the Jumihaidokuto + antihistamine group.

Response to therapy varies markedly among CSU patients, and patients' adherence to the recommended regimen is significantly affected by their experience of the drug's effectiveness.[15] Thus, the increased magnitude of improvement seen in CSU patients that were treated with Jumihaidokuto is expected to increase their adherence to the protocol.

In this study, subjects who did not experience symptom relief using the standard dose of antihistamines were enrolled. Therefore, the significant improvement in disease severity observed in the antihistamine group was an unexpected result for us. We speculate that enrollment in this clinical study motivated subjects to treat their CSU, and they may have adhered more closely to the dosing regimen. On the other hand, a favorable effect of Jumihaidokuto on the severity score was found after 8 weeks of treatment. Perhaps we should recommend that patients take Jumihaidokuto for at least 8 weeks to gain the clinical benefits.

It was also unexpected that the itch and the subjects' subjective symptom scores would be similar between the two groups. This result conflicted with the severity scores. However, this discrepancy may be due to the fact that these assessments

examine different disease features. The Japanese Dermatological Association severity scores mainly evaluate the level of a disabling condition, discomfort, and annoyance, whereas the questionnaire for subjective symptoms evaluates the frequency and intensity of both itch and wheals. Based on the discussion above, although antihistamines alone had some efficacy in treating patients with CSU, Jumihaidokuto might augment the therapeutic effect of antihistamine on the patients' disabling condition.

The limitations of this study were the small sample size of subjects and the lack of a treatment group receiving Jumihaidokuto only. In spite of these limitations, there are many cases of difficult-to-treat CSU, and Jumihaidokuto may have value for these suffering patients.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

KI and HM had made study protocol. KI had randomized the study subjects. HA and HM had contributed to intervention, and accumulated the clinical data. HM performed statistical analysis and wrote this manuscript.

Electronic Supplementary Material: Supplementary material (Appendixes 1 and 2) is available in the online version of this article at http://dx.doi.org/10.1007/s11655-017-2950-6.

REFERENCES

1. Hide M, Hiragun T, Japanese Dermatological A. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. Allergol Int 2012;61:517-527.
2. Murota H, Kitaba S, Tani M, Wataya-Kaneda M, Azukizawa H, Tanemura A, et al. Impact of sedative and non-sedative antihistamines on the impaired productivity and quality of life in patients with pruritic skin diseases. Allergol Int 2010;59:345-354.
3. Murota H, Kitaba S, Tani M, Wataya-Kaneda M, Katayama I. Effects of nonsedative antihistamines on productivity of patients with pruritic skin diseases. Allergy 2010;65:929-930.
4. Zhong H, Song Z, Chen W, Li H, He L, Gao T, et al. Chronic urticaria in Chinese population: a hospital-based multicenter epidemiological study. Allergy 2014;69:359-364.
5. Powell RJ, Leech SC, Till S, Huber PA, Nasser SM, Clark AT, et al. BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy 2015;45:547-565.
6. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. Methods report on the development of the 2013 revision and update of the EAACI/GA2 LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2014;69:e1-e29.
7. Altrichter S, Koch K, Church MK, Maurer M. Atopic predisposition in cholinergic urticaria patients and its implications. J Eur Acad Dermatol Venereol 2016;30:2060-2065.
8. Bailey E, Shaker M. An update on childhood urticaria and angioedema. Curr Opin Pediatr 2008;20:425-430.
9. Long JW, Wang YY, Pi XM, Tu YT. Clinical observation on the treatment of chronic urticaria with total glucosides of paeony capsule combined with citirizine. Chin J Integr Med 2010;16:353-356.
10. Koseki J, Matsumoto T, Matsubara Y, Tsuchiya K, Mizuhara Y, Sekiguchi K, et al. Inhibition of rat 5alpha-reductase activity and testosterone-induced sebum synthesis in hamster sebocytes by an extract of *Quercus acutissima* Cortex. Evid Based Complement Alternat Med 2015;2015:853846.
11. Matsumoto T, Matsubara Y, Mizuhara Y, Sekiguchi K, Koseki J, Tsuchiya K, et al. Plasma pharmacokinetics of polyphenols in a traditional Japanese medicine, jumihaidokuto, which suppresses propionibacterium acnes-induced dermatitis in rats. Molecules 2015;20:18031-18046.
12. Sekiguchi K, Koseki J, Tsuchiya K, Matsubara Y, Iizuka S, Imamura S, et al. Suppression of propionibacterium acnes-induced dermatitis by a traditional Japanese medicine, Jumihaidokuto, modifying macrophage functions. Evid Based Complement Alternat Med 2015;2015:439258.
13. Hashiro M, Matsumoto C, Takijiri C, Kitaba S, Murota H, Katayama I. Effect of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) on dermatological symptoms of patients with atopic dermatitis evaluation of eruption elements. Skin Res 2011;10:34-40.
14. Okawa A. Clinical efficacy of combination treatment of Ketotifen (HC 20-511) with harbal medicines on chronic urticaria. Med Consult New Remed 1987;24:923-930.
15. Kaneko S, Masuda K, Hiragun T, Inomata N, Furue M, Onozuka D, et al. Transient improvement of urticaria induces poor adherence as assessed by Morisky Medication Adherence Scale-8. J Dermatol 2015;42:1078-1082.

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