

ORIGINAL RESEARCH ARTICLE

## The Use of Oral Herbal Medicine (Hange-Shashin-To) in Patients with Pouchitis: A Pilot Study

Hiroki Matsuoka<sup>1,2)</sup>, Motoi Uchino<sup>2)</sup>, Yuki Horio<sup>2)</sup>, Hirofumi Sasaki<sup>2)</sup>, Teruhiro Chohno<sup>2)</sup>, Akihiro Hirata<sup>2)</sup>, Toshihiro Bando<sup>2)</sup>, Takashi Ito<sup>1)</sup>, Toshimasa Yamaguchi<sup>1)</sup> and Hiroki Ikeuchi<sup>2)</sup>

1) *Department of Surgery, Nishiwaki Municipal Hospital, Hyogo, Japan*  
2) *Inflammatory Bowel Disease Center, Hyogo College of Medicine, Hyogo, Japan*

### Abstract:

**Objectives:** Hange-Shashin-To (HST), which is a combination of seven herbs, has previously been used in the treatment of inflammatory or ulcerative gut disease. The aim of this study was to evaluate the safety and efficacy of HST for the treatment of chronic pouchitis. **Methods:** Nineteen patients with chronic pouchitis, defined as either frequent episodes ( $\geq$  three episodes per six months) of pouchitis or persistent symptoms that required continuous antibiotic therapies, were selected and treated with ciprofloxacin (CPFX) 600 mg/day for 2 weeks (week 0~2) and HST 3,750 mg/day for 32 weeks (week 0~32). The Pouchitis Disease Activity Index (PDAI) score was measured at week 0 and 6 for short-term evaluation. For long-term evaluation, total CPFX dose in the 26-week period prior to study entry (from 30 weeks before study entry to 5 weeks before study entry) was compared with the total CPFX dose during the 26-week study period (week 7~32). Although no concomitant administration of CPFX was permitted from week 2-6, patients whose condition deteriorated were prescribed CPFX from week 7 to week 32. **Results:** Fourteen patients completed this 32-week study. The PDAI scores of eight patients decreased below seven. The mean total PDAI scores decreased significantly from  $11 \pm 2.5$  to  $6.5 \pm 2.5$  ( $P < 0.001$ ). The mean value of total CPFX dose decreased significantly from  $491.6 \pm 182.4$  mg/kg to  $392.5 \pm 184.0$  mg/kg ( $P < 0.05$ ). No severe adverse events were noted. **Conclusions:** Our data suggest that HST has a positive effect on chronic pouchitis with no adverse effects.

### Keywords:

ulcerative colitis, pouchitis, herbal medicine, Hange-Shashin-To

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### Introduction

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the standard operation for patients with ulcerative colitis (UC). This procedure significantly improves patients' quality of life. However, many patients display significant postsurgical morbidity.

Pouchitis, which is defined as a nonspecific and idiopathic inflammation of the ileal pouch, is the most common complication after IPAA. The etiology of pouchitis,

like that of UC itself, is unclear. However, clinical and experimental studies suggest that the relative balance of aggressive and protective bacterial species is altered in UC and pouchitis. An overly-aggressive immune response to a subset of commensal enteric bacteria in genetically predisposed individuals because of this imbalance is thought to contribute to the development of these diseases<sup>1)</sup>. Therefore, antimicrobial therapy with antibiotics is considered first-line therapy for pouchitis treatment. However, in cases of antibiotic-refractory pouchitis, subsequent treatment, such as corti-

costeroids, immunosuppressive agents, and infliximab, has been challenging<sup>2-5</sup>.

In China, traditional Chinese herbal medicine has been administered for thousands of years<sup>6</sup>. In the 5<sup>th</sup> and 6<sup>th</sup> centuries, it was imported to Japan. This medicine developed independently and became Japanese traditional Kampo medicine. Hange-Shashin-To (HST), which is a combination of seven herbs (*Pinelliae Tuber*, *Scutellariae Radix*, *Glycyrrhizae Radix*, *Zizyphi Fructus*, *Ginseng Radix*, *Zingiberis Scitatum Rhizoma*, and *Coptidis Rhizoma*), is one such Kampo medicine. In Japan, HST has previously been used in the treatment of inflammatory or ulcerative gut diseases, especially the treatment of gastrointestinal disorders such as acute and chronic gastrointestinal catarrh, fermentative diarrhea, and acute gastroenteritis<sup>7</sup>. In addition, HST is used in treatment of chemotherapy-induced oral mucositis and diarrhea, and has demonstrated a significant effect<sup>8-10</sup>. However, although there are many reports in the Japanese literature concerning the use of HST, few reports are available in English.

The main symptom of pouchitis is diarrhea, therefore we hypothesized that HST could be an effective treatment in patients with chronic pouchitis. The aim of this pilot study was to evaluate the safety and efficacy of HST for the treatment of chronic pouchitis.

## Methods

### Ethical Considerations

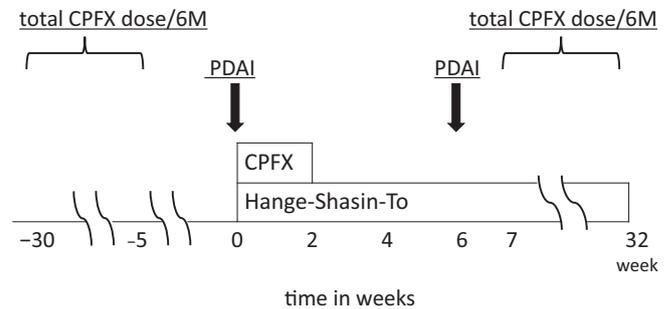
This study was approved by the Institutional Review Board of Hyogo College of Medicine, and written informed consent was obtained from all patients (No.1401). The study protocols were registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR000010004).

### Study design

We hypothesized that HST could be an effective treatment for patients with chronic pouchitis. The aim of this study was to evaluate the safety and efficacy of HST for the treatment of chronic pouchitis in a single-center, prospective, pilot study. The trial was conducted at the Inflammatory Bowel Disease Center of Hyogo College of Medicine between February 1, 2013 and August 31, 2014.

### Patient selection

Only patients who had undergone IPAA were eligible for this study. A second inclusion criterion stipulated only patients with chronic pouchitis; this was defined as frequent episodes ( $\geq$  three episodes per six months) of pouchitis. The diagnosis of pouchitis was based on the Pouchitis Disease Activity Index (PDAI), which comprised symptoms, endo-



**Figure 1.** Patients were treated with CPFX for 2 weeks (week 0~2) and HST for 32 weeks (week 0~32). The change of PDAI score and total CPFX dose were measured as evaluations. CPFX, ciprofloxacin; PDAI, Pouchitis Disease Activity Index.

scopic findings, and histological appearance<sup>11</sup>). Patients with a PDAI score of seven or higher were classified as having pouchitis upon study entry.

The following patient exclusion criteria were applied: 1) current use (within four weeks of this study entry) of antibiotics, 5-aminosalicylic acid products, immunomodulators, corticosteroids, biologics, or Japanese herbal medicine; 2) prescription of antibiotics in addition to ciprofloxacin (CPFEX) during the period from 30 weeks before study entry to 5 weeks before study entry; 3) evidence of Crohn's disease or cuffitis; 4) pregnancy, breast-feeding, or planning for a pregnancy during the study period; 5) pouchitis triggered by *Clostridium difficile*, cytomegalovirus, or any other infectious enteritis.

### Study protocol

Patients with chronic pouchitis were treated with CPFEX 600 mg/day for 2 weeks (week 0~2) and HST (Hange-Shashin-To, Tsumura Inc., Tokyo) 3,750 mg/day for 32 weeks (week 0~32) (Figure 1). *Bifidobacterium bifidum* (BIO-THREE<sup>®</sup>, TOA SHINYAKU Inc., Tokyo) 1,200 mg/day was used concomitantly in all patients before and during this study. No concomitant administration of 5-aminosalicylic acid, corticosteroids, immunomodulators, biologics, and antibiotics except CPFEX was permitted during the administration of HST. No concomitant administration of CPFEX was permitted from week 2-6; however, any patient whose condition had deteriorated was prescribed CPFEX from week 7-32. Specifically, in comparison with the remission, when clinical subscores of PDAI increased at least two points for five days straight, we prescribed CPFEX for two weeks.

### Diagnostic criteria and evaluation

Pouch endoscopy with biopsies was conducted immediately prior to commencement of the treatment (week 0) and repeated in week 6; the change of PDAI score during this period was computed to provide a short-term evaluation. A

**Table 1.** Clinical Characteristics of Patients.

Case	Age (years)	Sex	Time since pouch function (months)	Time since onset of pouchitis (months)	Duration of this study (weeks)
1	53	F	10.8	8.8	32
2	46	M	57.4	22.2	32
3	52	F	33.5	30.1	32
4	41	M	10.1	8.1	32
5	68	F	71.6	35.7	32
6	62	M	214.5	13.2	32
7	39	M	125.3	41.6	32
8	36	F	33.8	17.0	32
9	43	M	12.2	9.2	32
10	66	M	18.0	13.0	32
11	36	F	10.4	8.4	32
12	59	M	43.6	18.2	32
13	38	F	38.5	25.6	32
14	35	M	39.9	34.8	32
15	32	M	21.8	13.3	until 8
16	40	M	160.4	10.9	until 5
17	44	M	15.6	9.4	until 4
18	30	M	67.8	58.8	until 5
19	58	M	10.5	9.2	until 16

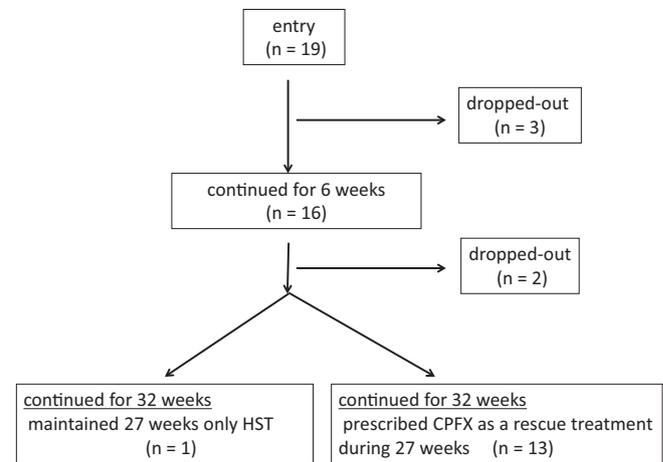
short-term responder (s-R) was defined as a patient with a total PDAI score of <7. A short-term partial responder (s-PR) whose total PDAI score was decreased from their original, but it is more than 7.

Furthermore, as the simplest evaluation, we interviewed and compared the defecation frequency per day in week 0, 2, 4, 6, and on a usual remission day.

For long-term evaluation, we compared total CPFX dose (mg/kg) for a 26-week period prior to study entry (from 30 weeks before study entry to 5 weeks before study entry) with that for a 26-week period during the study period (from week 7 to week 32 after study entry). During the latter 26 weeks, a long-term responder (l-R) was defined as a patient who did not need CPFX, while a long-term partial responder (l-PR) was defined as a patient for whom the total CPFX dose had decreased.

Moreover, we added to compare total CPFX dose during a 26-week period from week 7 to week 32 after the former incidence of pouchitis before study entry.

Laboratory tests and physical examinations were performed at week 0, 2, 4, 6, and 32. The laboratory tests evaluated inflammatory markers (C-reactive protein, CRP; erythrocyte sedimentation rate, ESR; and procalcitonin, PCT), liver function, renal function, glucose tolerance, and complete blood count. The tests included complete blood counts, aspartate transaminase, alanine transaminase,  $\gamma$ -glutamyl transpeptidase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, chloride, and blood glucose



**Figure 2.** Flow diagram of participant enrollment in this study. HST, Hange-Shashin-To; CPFX, ciprofloxacin.

levels.

### Statistical analysis

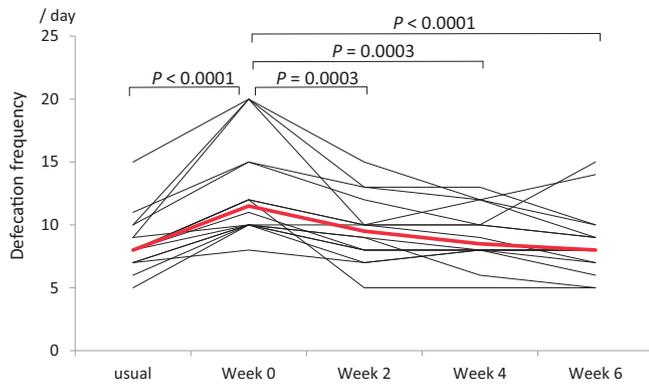
The Wilcoxon matched pairs test and two-tailed Student *t*-test were used for statistical analysis. A 2-sided *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with JMP<sup>®</sup> 11 (SAS Institute Inc., Cary, NC, USA).

## Results

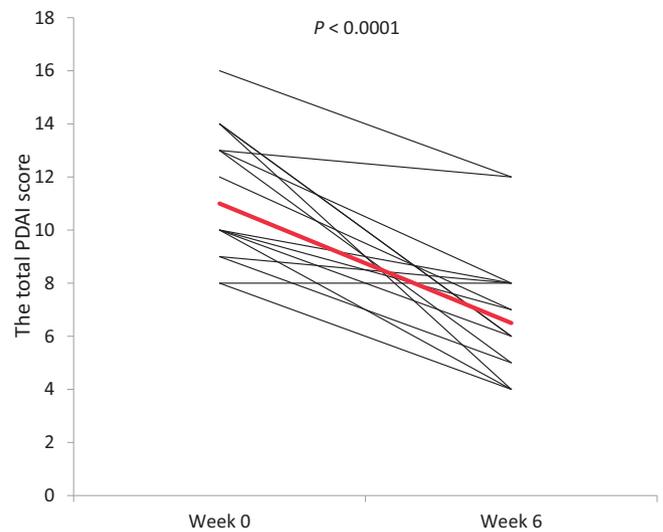
### Baseline characteristics

Nineteen patients in total with chronic pouchitis were enrolled in this study. Of these patients 68% were male (13 male, 6 female) and the mean age was 43 (range 30-68) years (Table 1). The mean time since onset of pouchitis was 13.3 (range 8.1-58.8) months. Previous treatment for pouchitis in all patients was CPFX only.

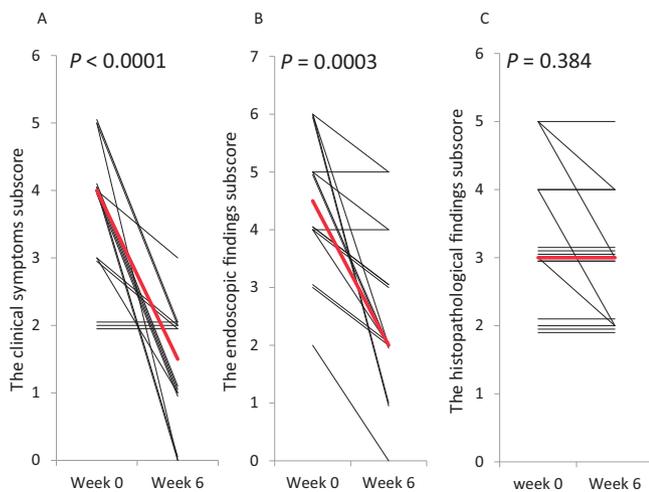
Sixteen patients completed the first six weeks and three patients dropped out. Two of these three patients were prescribed antibiotics due to recurrence of pouchitis, while one patient could not tolerate the taste of HST. Fourteen of the remaining 16 patients continued for 32 weeks; the other 2 patients dropped out. Again, the two patients who dropped out could not tolerate the taste. Only 1 patient continued until week 32 without taking antibiotics. Thirteen patients who continued until week 32 were temporarily prescribed antibiotics when symptoms of pouchitis developed between week 7 and week 32 (Figure 2). The only antibiotic prescribed in the 26-week period to week 0 was CPFX. Moreover, the only antibiotic prescribed as a rescue treatment from week 7 to 32 was CPFX.



**Figure 3.** The defecation frequency in each patient. The red line denotes the median value.



**Figure 5.** The total PDAI score at week 0 and week 6. The red line denotes the median scores. PDAI, Pouchitis Disease Activity index.



**Figure 4.** The PDAI subscores at week 0 and 6. The red line denotes the median scores. The clinical symptoms subscores (A); the endoscopic findings subscores (B); the histopathological findings subscores (C). PDAI, Pouchitis Disease Activity index.

**Defecation frequency**

The defecation frequency in each patient is shown in Figure 3. The median values of defecation frequency were 8 times per day (range 6-15) on a usual remission day, 12 times per day (range 8-20) at week 0, 9.5 times per day (range 5-15) at week 2, 8.5 times per day (range 5-13) at week 4, and 8 times per day (range 5-15) at week 6. The defecation frequency at week 0 was significantly higher than usual ( $P < 0.01$ ). The defecation frequencies at weeks 2, 4 and 6 were significantly lower than the defecation frequency at week 0 ( $P < 0.01$ ).

**PDAI**

The mean PDAI scores immediately prior to treatment were as follows: clinical subscores of  $4 \pm 1$  (range 2-5); endoscopic inflammation subscores of  $4.5 \pm 1.2$  (range 2-6); acute histologic inflammation subscores of  $3 \pm 1.1$  (range 2-

5); and total PDAI scores of  $11 \pm 2.5$  (range 8-16). The mean PDAI scores at week 6 were: clinical subscores of  $1.5 \pm 0.9$  (range 0-3); endoscopic inflammation subscores of  $2 \pm 1.4$  (range 0-5); acute histologic inflammation subscores of  $3 \pm 0.9$  (range 2-5); and total PDAI scores of  $6.5 \pm 2.5$  (range 4-12) (Figure 4, 5). The mean PDAI scores, clinical subscores, and endoscopic inflammation subscores at week 6 were significantly lower than those observed at week 0. There were no significant differences in subscores of histopathological findings between week 0 and week 6. Eight of the 19 treated patients were classified as short-term responders (s-R) (42%) and seven patients were classified as short-term partial responders (s-PR) (37%) (Figure 6A). Three of the four patients classified as short-term others (s-others) dropped out from the study; the scores of the other patient did not change.

**Total CPFX dose**

The changes in total CPFX dose between a 26-week period before study entry (from 30 weeks before study entry to 5 weeks before study entry) and a 26-week period after study entry (from week 7 to week 32) are shown in Figure 7A. The mean value decreased significantly from  $491.6 \pm 182.4$  mg/kg (range 341.4-954.5) during the pre-study 26-week period to  $392.5 \pm 184.0$  mg/kg (range 0-680.1) during the 26-week period of the study ( $P = 0.034$ ). According to our definition, one of 19 treated patients was characterized as a long-term responder (l-R) (5%), and eight patients were characterized as long-term partial responders (l-PR) (42%). Among the 10 patients classified as long-term others (l-others), two patients showed no change, the mean value increased in three patients, and five patients dropped out (Fig-

ure 6B).

The changes in total CPMX dose between a 26-week period from week 7 to week 32 after the previous pouchitis before study entry and a 26-week period after study entry (from week 7 to week 32) are shown in Figure 7B. Three of 14 patients were unable to compare because time since onset of pouchitis was short. In comparison with a 26-week period after study entry (from week 7 to week 32), total CPMX dose of 8 cases decreased, one case increased, and two cases did not change. The mean value decreased significantly from 631.5 ± 371.1 mg/kg (range 113.8-1145.5) during the pre-study 26-week period (from week 7 to week 32 after the previous occurrence of pouchitis) to 442.1 ± 184.6 mg/kg (range 0-579.3) during the 26-week period of the study ( $P = 0.025$ ).

**Laboratory tests and safety**

Table 2 shows the values of inflammatory markers.

The mean procalcitonin (PCT) values decreased significantly from 0.07 ± 0.1 (range 0-0.38) at week 0 to 0.03 ± 0.04 (range 0-0.15) at week 2 and 0.04 ± 0.08 (range 0-0.33) at week 4 ( $P < 0.05$ ). There was no significant difference between PCT values at week 0 and week 6.

The mean C-reactive protein (CRP) values decreased significantly from 2.5 ± 3.1 (range 0-8.6) at week 0 to 0.3 ± 0.2 (range 0-0.7) at week 2, 0.4 ± 0.6 (range 0-2.6) at week 4, and 0.7 ± 1.2 (range 0-4.4) at week 6. There were no sig-

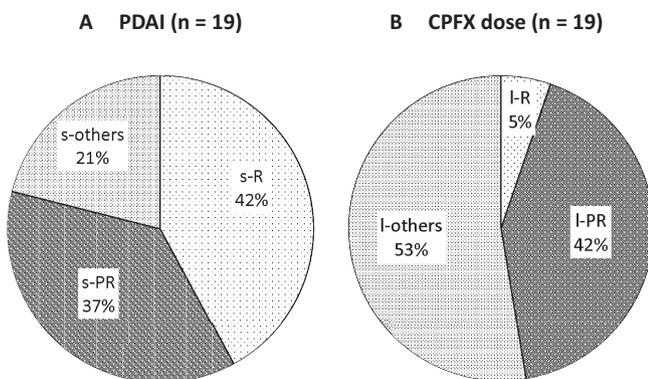
nificant differences in CRP values between weeks 2, 4, and 6.

Like CRP, the mean erythrocyte sedimentation rate (ESR) values decreased significantly from 28 ± 23 (range 3-81) at week 0 to 17±12 (range 2-46) at week 2, 17 ± 14 (range 2-60) at week 4, and 19 ± 18 (range 2-69) at week 6. There were no significant differences between ESR values in week 2, 4, and 6.

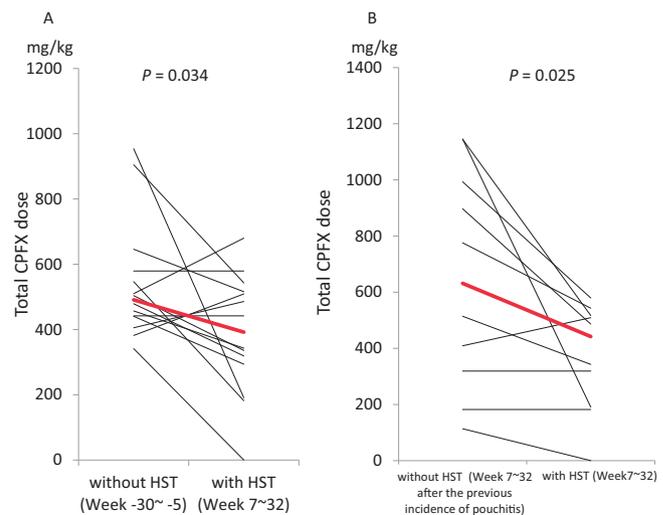
The results of all laboratory tests, including complete blood counts, liver function, renal function, electrolyte levels, and blood glucose levels, are shown in Table 3. No significant adverse drug-related effects were reported during this study.

**Discussion**

A number of different medicines, including 5-aminosalicylate, steroid, immunomodulators, and antitumor



**Figure 6.** The changes of total PDAI scores (A) and CPMX dose (B). s-R, short-term responder; s-PR, short-term partial responder; s-others, short-term others; I-R, long-term responder; I-PR, long-term partial responder; I-others, long-term others.



**Figure 7.** A: The changes in total CPMX dose during a 26-week period before study entry (from 30 weeks before study entry to 5 weeks before study entry) and a 26-week period after study entry (from week 7 to week 32). B: The changes in total CPMX dose during a 26-week period from week 7 to week 32 after the former incidence of pouchitis before study entry and a 26-week period after study entry (from week 7 to week 32). The red line denotes the median total CPMX dose. CPMX, Ciprofloxacin; HST, Hange-Shashin-To.

**Table 2.** Inflammatory Marker Results.

	Week 0	Week 2	P	Week 4	P	Week 6	P
PCT, ng/ml	0.07±0.09	0.03±0.03	0.02	0.04±0.08	0.04	0.03±0.02	N.S
CRP, mg/dl	2.5±3.1	0.3±0.2	0.01	0.4±0.6	0.01	0.7±1.2	0.03
ESR, mm/1h	28±23	17±12	<0.01	17±14	<0.01	19±17	0.02

PCT, procalcitonin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

**Table 3.** Results of the Laboratory Tests.

	Week 0	Week 6	P	Week 32	P
WBC, / $\mu$ L	6530 $\pm$ 1652	6955 $\pm$ 1591	0.69	6480 $\pm$ 1459	0.09
RBC, $\times$ 1000/ $\mu$ L	465 $\pm$ 44.1	462 $\pm$ 55.1	0.91	463 $\pm$ 45.3	0.27
Hb, g/dl	13.9 $\pm$ 1.7	13.8 $\pm$ 1.8	0.69	13.4 $\pm$ 1.1	0.29
Ht, %	41.2 $\pm$ 3.9	39.9 $\pm$ 4.0	0.73	40.2 $\pm$ 2.7	0.27
Plt, $\times$ 1000/ $\mu$ L	23.0 $\pm$ 7.3	22.9 $\pm$ 8.5	0.81	23.4 $\pm$ 7.9	0.41
AST, IU/L	18 $\pm$ 16.5	17.5 $\pm$ 8.6	0.17	18 $\pm$ 5.3	0.11
ALT, IU/L	12 $\pm$ 5.7	11.5 $\pm$ 12.9	0.08	14.5 $\pm$ 8.8	0.10
$\gamma$ -GTP, IU/L	26 $\pm$ 47.5	28.5 $\pm$ 29.6	0.14	27.5 $\pm$ 23.3	0.052
T-BIL, mg/dl	0.6 $\pm$ 0.4	0.6 $\pm$ 0.2	0.80	0.7 $\pm$ 0.3	0.92
BUN, mg/dl	13 $\pm$ 3.8	12 $\pm$ 4.3	0.89	13.5 $\pm$ 4.3	0.77
Cre, mg/dl	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2	0.08	0.7 $\pm$ 0.2	0.08
Na, mEq/L	140.5 $\pm$ 3.3	140 $\pm$ 2.1	0.36	140.5 $\pm$ 2.1	0.94
K, mEq/L	4.2 $\pm$ 0.3	4.2 $\pm$ 0.3	0.84	4.1 $\pm$ 0.3	0.13
Cl, mEq/L	104 $\pm$ 3.6	105 $\pm$ 2.8	0.24	105 $\pm$ 2.8	0.95
BS, mg/dl	100 $\pm$ 17.5	100 $\pm$ 13.6	0.14	97 $\pm$ 14.2	0.06

Numerical data are given as the mean value with the standard deviation.

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase;  $\gamma$ -GTP,  $\gamma$ -glutamyl transpeptidase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; BS, blood sugar

necrosis factor monoclonal antibody, have been routinely prescribed for the treatment of UC. Nonetheless, complementary and alternative medicines for the treatment of UC have attracted considerable attention. Traditional Chinese medicine holds a prominent position in the field of complementary and alternative medicine. In recent years, traditional Chinese medicine has found widespread acceptance outside of East Asia. It has been estimated that 28.9% of adults in the US regularly use one or more traditional Chinese medicine therapies, 9.6%-12.1% of which are in the form of herbal products<sup>12</sup>. Sałaga et al. (2014) have summarized previous human studies concerning the use of Chinese herbal medicines in the treatment of inflammatory bowel disease (ulcerative colitis, six articles; inflammatory bowel disease, two articles)<sup>13</sup>. However, reports concerning herbal medicines are largely outnumbered by articles reporting conventional treatment for pouchitis.

A major symptom of pouchitis is diarrhea. The level of prostaglandin E2 (PGE2) in the digestive tract plays an important role in diarrhea. Thus, PGE2 enhances intestinal peristalsis, inhibits Na<sup>+</sup> absorption by interfering with the Na<sup>+</sup>, K<sup>+</sup>-ATPase activity, enhances Cl<sup>-</sup> secretion, and reduces water absorption, leading to diarrhea<sup>14,15</sup>. Evidence has been presented that *Glycyrrhizae Radix* and *Zingiberis Sciatum Rhizoma*, which are components of HST, suppress PGE2<sup>16-18</sup>. Moreover, Vento et al. (2011) reported that Cyclooxygenase-2 (COX-2) expression is positively correlated with mucosal atrophy in patients with chronic pouchitis<sup>19</sup>. COX-2 is an important enzyme in the control of PGE2 production. Together, these results suggest that HST may be useful in the

treatment of pouchitis. One of the recommended cures for antibiotic-refractory pouchitis is steroids, and several studies have reported their effectiveness<sup>2,3</sup>. It is interesting to note that glycyrrhizin, a chief ingredient of *Glycyrrhizae Radix* (one of the constituent crude drugs of HST), is transformed to glycyrrhetic acid by intestinal bacteria and is then absorbed. Glycyrrhizin and glycyrrhetic acid primarily inhibit 11 $\beta$ -HSD-2, which itself inactivates cortisol. Thus, by indirectly increasing levels of cortisol, glycyrrhizin may present an anti-inflammatory effect<sup>20,21</sup>.

By comparison with week 0, the mean PDAI scores at week 6 are significantly improved. However, with regard to the short-term evaluation, the influence of CPF<sub>X</sub> within the first two weeks cannot be contested. Although a simple comparison is not accurate, according to the study of CPF<sub>X</sub> for acute pouchitis, all seven patients (100%) in the CPF<sub>X</sub> group achieved resolution of pouchitis as defined by a post-treatment PDAI score less than seven at two weeks<sup>22</sup>.

With regard to the long-term evaluation, only 1 of the 19 cases did not require antibiotic rescue during the post-study entry 26-week period. However, a significant difference was observed in the mean total CPF<sub>X</sub> dose required after treatment. Although HST treatment for pouchitis does not produce a dramatic effect, a positive effect has been observed.

In general, misuse and overuse of antibiotics have both contributed to antibiotic resistance. Moreover, Velicer et al. (2004) have suggested that long-term use of antibiotics is associated with increased risk of incidental and fatal breast cancer<sup>23</sup>. By administering HST for chronic pouchitis, the total mean dose of antibiotics may be reduced and the side

effects of antibiotics may thus decrease.

No significant adverse effects were reported during our six-month study. Although the prevalence has not been quantified, side effects of HST included liver function failure, pseudohyperaldosteronism, and interstitial pneumonia. Thus, HST should not be administered aimlessly in the long term (and follow-up laboratory tests and radiography should be performed as appropriate). In the present study, three of 19 patients dropped out of this study because of the distinctive flavor of HST. It may be advisable to create a new flavor for improving medical compliance.

There are several limitations to our study. First, because of the uncontrolled nature of the study, it is difficult to evaluate the efficacy of HST independently. To eliminate the influence of fixed CPFx for 2 weeks after study entry, we added to compare total CPFx dose during a 26-week period after the former incidence of pouchitis before study entry. This study was originally small sample size with single arm. In addition, the number of cases that was able to be compared was even smaller. Second, according to the "Patient selection," previous treatments may have affected the results. However, during the period from 30 weeks before study entry to 5 weeks before study entry, all 19 patients were administered only CPFx for pouchitis. In any case, more rigorous and well-designed controlled or comparative trials involving a larger cohort are needed to confirm these findings.

In conclusion, although there was no dramatic effect that substituted for antibiotics in the treatment of pouchitis, our results suggest that HST is able to reduce the CPFx dose and does not induce adverse reaction.

#### Conflicts of Interest

There are no conflicts of interest.

#### Source of Funding

No funding was provided for this case series.

#### References

- Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. *Gastroenterology*. 2004 May; 126: 1620-33.
- Navaneethan U, Venkatesh PG, Bennett AE, et al. Impact of budesonide on liver function tests and gut inflammation in patients with primary sclerosing cholangitis and ileal pouch anal anastomosis. *J Crohn's Colitis*. 2012 Jun; 6: 536-42.
- Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther*. 2007 May; 25: 1231-6.
- Winter TA, Dalton HR, Merrett MN, et al. Cyclosporin A retention enemas in refractory distal ulcerative colitis and 'pouchitis'. *Scand J Gastroenterol*. 1993 Jan; 28: 701-4.
- Acosta M, Bosch O, Souto R, et al. Efficacy of infliximab rescue therapy in patients with chronic refractory pouchitis: a multicenter study. *Inflamm Bowel Dis*. 2012; 18: 812-7.
- Flaws B, Sionneau P. The treatment of modern Western medical diseases with Chinese medicine: a textbook & clinical manual. Boulder, CO:Blue Poppy Enterprises, Inc; 2001.
- Kawashima K, Nomura A, Makino T, et al. Pharmacological properties of traditional medicine (XXIX): effect of Hange-shashin-to and the combinations of its herbal constituents on rat experimental colitis. *Biol Pharm Bull*. 2004; 27: 1599-603.
- Matsuda C, Munemoto Y, Mishima H, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hange-shashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemother Pharmacol*. 2015 Jul; 76: 97-103.
- Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (Hangeshashinto) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol*. 2003 May; 51: 403-6.
- Komatsu Y, Yuki S, Fuse N, et al. Phase 1/2 clinical study of irinotecan and oral S-1 (IRIS) in patients with advanced gastric cancer. *Adv Ther*. 2010 Jul; 27: 483-92.
- Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc*. 1994 May; 69: 409-15.
- Comar KM, Kirby DF. Herbal remedies in gastroenterology. *J Clin Gastroenterol*. 2005 July; 39: 457-68.
- Sařaga M, Zatrski H, Sobczak M, et al. Chinese Herbal Medicines in the Treatment of IBD and Colorectal Cancer: A Review. *Curr Treat Options Oncol*. 2014 Sep; 15: 405-20.
- Argenzio RA, Lecce J, Powell D. Prostanoids Inhibit Intestinal NaCl Absorption in Experimental Porcine Cryptosporidiosis. *Gastroenterology*. 1993 Sep; 104: 440-7.
- Cohen-Luria R, Rimon G, Moran A. PGE2 inhibits Na-K-ATPase activity and ouabain binding in MDCK cells. *Am J Physiol Renal Physiol*. 1993 Jan; 264: F61-5.
- Kiuchi F, Shibuya M, Sankawa U. Inhibitors of Prostaglandin Biosynthesis from Ginger. *Chem Pharm Bull*. 1982 Feb; 30: 754-7.
- Sankawa U. Inhibitions of prostaglandin biosynthesis contained in Chinese medicinal drugs. *Igaku no Ayumi*. 1983; 126: 867-974.
- Suekawa M, Yuasa L, Isono M, et al. Pharmacological studies on ginger. IV. Effect of (6)-shogaol on the arachidonic cascade. *Nihon yakurigaku zasshi Folia pharmacologica Japonica*. 1986 Oct; 88: 263-9.
- Vento P, Lepistö A, Kärkkäinen P, et al. Risk of cancer in patients with chronic pouchitis after restorative proctocolectomy for ulcerative colitis. *Colorectal Dis*. 2011 Jan; 13: 58-66.
- Fiore C, Eisenhut M, Ragazzi E, et al. A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol*. 2005 Jul; 99: 317-24.
- Baltina LA. Chemical modification of glycyrrhizic acid as a route to new bioactive compounds for medicine. *Curr Med Chem*. 2003 Jan; 10:155-71.
- Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis*. 2001 Nov; 7: 301-5.
- Velicer CM, Heckbert SR, Lampe JW, et al. Antibiotic use in relation to the risk of breast cancer. *Jama*. 2004 Feb; 291: 827-35.