—Articles—

A Comparative Study of the Usefulness of *Toki-shakuyaku-san* and An Oral Iron Preparation in the Treatment of Hypochromic Anemia in Cases of Uterine Myoma

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We prospectively studied and compared the usefulness of Kampo medicine (Sino-Japanese traditional herbal medicine) ''*Toki–shakuyaku–san*'' and an oral iron preparation in the treatment of hypochromic anemia associated with uterine myoma. The study subjects consisted of 25 patients who were diagnosed as having hypochromic mild to moderate anemia associated with menorrhagia attributable to uterine myoma. They were divided into the *Toki–shakuyaku–san* group ($n=10$) and the oral iron group ($n=15$). We monitored the blood counts, subjective symptoms, and occurrence of side effects after oral administration of either preparation for 4 and 8 weeks in these subjects. In regard to the blood counts and improvement of the laboratory parameters of anemia, while marked improvement was observed in the oral iron group, no significant improvement was noted in the *Toki–shakuyaku–san* group. On the other hand, in terms of improvement of the signs and symptoms of anemia, such as facial pallor, spoon-shaped nails and dizziness, the latter group also showed significant improvement. In addition in the *Toki–shakuyaku–san* group, resolution of symptoms such as hypermenorrhea, dysmenorrhea, feeling cold, dizziness, headache and shoulder stiffness was also noted. While side effects were encountered in 80.0% of patients in the oral iron group, no significant side effects were observed in the *Toki–shakuyaku–san* group. From these findings, it is considered that *Toki–shakuyaku–san* may be useful for resolving the symptoms of mild or moderate anemia associated with uterine myoma.

Key words——*Toki–shakuyaku–san*; iron preparation; anemia; uterine myoma

INTRODUCTION

Iron supplements are widely prescribed for the treatment of iron deficiency anemia.[1,2] Indiscriminate use of oral iron, however, may cause hemochromatosis or cell injury,[3] furthermore, the high frequency of gastrointestinal side effects reduces the medication compliance rate of the patients. Since combined prescription of iron tablets and a drug to counteract the gastrointestinal side effects would increase the medical care expenditure,[4] appropriate use of oral iron preparation is nowadays required. In a previous study, we retrospectively examined the effects, safety and cost-effectiveness of *Toki–shakuyaku–san*, Kampo medicine (Sino-Japanese traditional herbal medicine), in the treatment of iron deficiency anemia, in comparison with those of an oral iron supplement and reported its favorable effects.[4] *Toki–shakuyaku–san* is composed of substances derived from 6 medicinal plants, including toki, senkyu, shakuyaku, sojutsu, takusha, and bukuryo. This Kampo medicine is known to be effective in the treatment of physically weak women with indefinite symptoms, perhaps because of its effects of inducing smooth muscle relaxation and facilitating hemopoiesis and adequate water level control in body.[5] *Toki–shakuyaku–san* is one of the most widely prescribed Kampo medicines for the treatment of gynecological disorders, such as infertility, dysmenorrhea and climacteric disturbances, in addition to being used for anemia.[6] Since the Kampo medicine has been confirmed to have no teratogenicity in animal experiments,[7] it has also been used in the treatment of hydremia of pregnancy.[5] Much,

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however, still remains unknown about the mechanism of actions of this Kampo medicine.

Uterine myoma is known to occur in 5 to 10 % of women in the reproductive age group, and 10 to 20 % of women over the age of 40 years.[8] The frequency of menorrhagia or dysmenorrhea is high (87.5%) in patients with uterine myoma,[9] and the resultant anemia and the symptoms associated with it substantially depress the quality of life (QOL) of these patients. Thus, treatment of patients with uterine myoma is important. But the efficacy and safety of *Toki–shakuyaku–san* has not been evaluated for anemia patients with uterine myoma, yet. In this prospective study, we compared the efficacy and safety of *Toki–shakuyaku–san* and an oral iron supplement in the treatment of anemia associated with menorrhagia in cases of uterine myoma, by assessing the improvements of the signs and symptoms and laboratory abnormalities induced by either drug in these patients.

SUBJECTS AND METHODS

Subjects The study were subjects who visited the Department of Obstetrics and Gynecology, Kitasato University Hospital as outpatients between August 1, 1999 and January 31, 2000, and it's subjects were diagnosed as having mild to moderate anemia (Hb 8.0 to 12.0 g/dl) associated with uterine myoma. The iron deficiency anemia was diagnosed at the value of RBC, Hb, Ht, MCV, MCH and MCHC. In total, 25 patients were enrolled in the study. All the patients gave informed consent for the use of their laboratory and clinical data for this prospective study. The patients were randomly assigned to one of two groups in the index mainly Hb value; the *Toki–shakuyaku–san* group ($n=10$), in which the patients received 2.5 g of *Toki–shakuyaku–san* extract granule (Tsumura Co., Ltd., Tokyo, Japan) thrice daily before meals, and the oral iron group ($n=15$), in which patients received one to two tablets of sodium ferrous citrate (Ferromia® tablets, Eisai Co., Ltd., Tokyo, Japan) daily after meals in 1 to 2 divided doses. Of the 25 patients enrolled in this study, severe side effects were encountered in 2 patients in the oral iron group. These two patients were excluded from the study at the discretion of the physician. The mean ($\pm$ SE) age was 45.40 ± 1.99 in the *Toki–shakuyaku–san* group ($n=10$), and 42.85 ± 1.68 in the oral iron group ($n=13$).

Parameters Examined The clinical severity of the uterine myoma was assessed by the attending physician. On the same day, hematological testing was performed to determine the total white blood cell count (WBC), differential white cell count, including eosinophils (EOS), lymphocytes (LYM), monocytes (MONO), basophils (BASO) and neutrophils (NEUTRO), the red blood cell count (RBC), hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, platelet count (PLT), prothrombin time (PT), and activated partial thromboplastin time (APTT). Blood biochemical tests were also carried out, to determine the serum levels of total protein (TP), albumin (Alb), total bilirubin (TB), direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), cholinesterase (CHE), lactate dehydrogenase (LDH), creatine kinase (CK), amylase (AMY), total cholesterol (TC), triglyceride (TG), blood urea nitrogen (BUN), creatinine (CR), uric acid (UA), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), phosphorus (P), iron (Fe), total iron-binding capacity (TIBC), and ferritin. These laboratory parameters were recorded on the clinical record form by a pharmacist involved in the study. The pharmacist also interviewed each patient to assess the signs and symptoms associated with iron deficiency anemia in these patients with uterine myoma and recorded the findings on the clinical record form (Table 1). Since *Toki–shakuyaku–san* is known to alleviate menopausal disturbances as well, symptoms of climacteric disturbances were additionally included in the interview items. The interview and it's items were decided after much discussion among the participating physicians and pharmacists. The observation period of the patients was 2 months. The clinical, hematological and blood biochemical parameter assessment was performed at baseline, and at 4 and 8 weeks after the start of the study treatment. The results were reported to the physician, and appropriate medical interventions were undertaken, if necessary. The changes in the study parameters over time were analyzed. The pharmacist also made enquiries about any side effects of the study drugs noted by the patient at 4 and 8 weeks after the start of the treatment, along with regular instruction on dosage and administration for ambulatory patients. Any abnor-

Table 1. Assessment of Signs and Symptoms in Patients with Anemia Associated with Uterine Myoma

	Clinical symptoms	Severity scale														
		Baseline					At 4 weeks					At 8 weeks				
Anemia-related																
1	Pallor	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
2	Spoon-shaped nails (koilonychias)	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
3	Soreness of the mouth and cracks at the angles	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4	Palpitation	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
5	Dizziness on standing (lightheadedness)	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
6	Difficulty in waking up	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
7	Easy fatigability, malaise	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
8	Shortness of breath	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
9	Swallowing difficulty	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
10	Deviant food habits	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
11	Feeling of thrusting of food on the tongue	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
12	Occult blood in feces	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Uterine-myoma-related																
1	Menstrual pain	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
2	Menorrhagia	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
3	Low back pain	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4	Lower abdominal pain	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
5	Constipation	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
6	Dysuria	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
7	Increased urinary frequency	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Climacteric symptoms																
1	Hot flushes	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
2	Bursts of sweating	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
3	Cold feeling in the lower part of the body	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4	Cold hands and feet	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
5	Dizziness	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
6	Nausea	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
7	Headache	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
8	Tinnitus	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
9	Shoulder stiffness	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
10	Tingling pain in the hands and feet	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
11	Leg cramps	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
12	Diarrhea	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
13	Bloated feeling	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
14	Edema	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
15	Insomnia	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
16	Shallow sleep	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
17	Irritability	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
18	Nervousness	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
19	Anxiety	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
20	Numbness in the hands and feet	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
21	Loss of feeling in the hands and feet	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
22	Formication	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4

Severityscale; 0 (none: score 0), 1 (slight: very slight and infrequent symptoms: score 1), 2 (mild: mild symptoms causing a little distress: score 2), 3 (moderate: moderate symptoms causing some distress: score 3), 4 (severe: severe symptoms that are difficult to tolerate, causing much distress and interference with daily activities: score 4).

mal findings were reported to the physician, who administered appropriate treatment where required.

Assessment of Signs and Symptoms For assessment of the signs and symptoms of anemia, 12 symptom parameters were included: pallor, spoon shape of the nails (koilonychias), soreness of the mouth and cracks at the angles, palpitations, dizziness on standing, difficulty in waking up, easy fatigability, malaise, shortness of breath, swallowing difficulty, deviant food habits, thrusting sensation of food on the tongue, and occult blood in the feces. The 7 symptom parameters of uterine myoma assessed were dysmenorrhea, menorrhagia, low back pain, lower abdominal pain, constipation, dysuria, and increased urinary frequency. The climacteric disturbance index was assessed from 22 symptoms, including hot flushes, bursts of sweating, cold feeling in the lower part of the body, cold hands and feet, dizziness, nausea, headache, tinnitus, shoulder stiffness, tingling pain in the hands and feet, leg cramps, diarrhea, bloated feeling, edema, insomnia, shallow sleep, irritability, formication, anxiety, numbness of the hands and feet, loss of feeling in the hands and feet, and nervousness. These signs and symptoms were scored on a scale of 0 to 4 as follows, at baseline and after 4 and 8 weeks of the study treatment: 0 (none), 1 (slight: very slight and infrequent symptoms), 2 (mild: mild symptoms causing a little distress), 3 (moderate: moderate symptoms causing some distress), and 4 (severe: severe symptoms that are difficult to tolerate, causing much distress and interference with daily activities) (Table 1).

Statistical Analysis Wilcoxon's rank-sum test was used to compare the improvement in the *Toki–shakuyaku–san* group and the oral iron group. Changes in the laboratory parameters and sings/symptoms over time were analyzed by Wilcoxon's signed-ranks test. $P<0.05$ was considered to denote statistical significance.

RESULTS

Laboratory Data The hematological and blood biochemical parameters indicative of the degree of anemia at baseline are shown in Table 2. No significant differences were noted between the two groups in terms of the RBC, Hb, Ht, reticulocyte count, MCV, MCH, MCHC, TIBC, or serum ferritin level at baseline. Since the serum Fe level at baseline was significantly higher in the *Toki–shakuyaku–san* group than in the oral iron group, changes in the serum Fe level relative to the baseline were compared between the two groups after 4 and 8 weeks of treatment. Concerning the blood biochemical parameters, no significant differences or abnormal values were found between the two groups in terms of the TP, Alb, TB, DB, AST, ALT, ALP, γ-GTP, CHE, LDH, CK, AMY, TC, TG, BUN, Cr, UA, Na, K, Cl, Ca, P, TIBC, or ferritin at baseline. Furthermore, no significant differences in the hematological and blood biochemical data at baseline were observed between patients who had subjective symptoms of anemia and patients who did not (Table 3).

Changes in Laboratory Findings over Time

The laboratory parameters indicative of the severity of anemia are shown in Table 2, together with other laboratory parameters that showed changes relative to the baseline levels after 4 and 8 weeks of the study treatment. In the *Toki–shakuyaku–san* group, while no changes in the Hb, Ht, MCV, MCH, and TIBC were observed, no deterioration of the anemic condition was observed either in any of the patients. Concerning the serum Fe level, the level at the baseline was significantly higher in the *Toki–shakuyaku–san* group than in the oral iron group, therefore changes relative to the levels at baseline were used for the analysis. While no significant changes from the baseline levels were observed in the serum Fe level in the *Toki–shakuyaku–san* group ($1\pm8\mu$g/dl after 4 weeks of the treatment and -10 ± 6 μg/dl after 8 weeks of treatment), the serum Fe levels showed significant increase in the oral iron group. This difference could, at least in part, be related to the serum Fe level at baseline being closer to the normal range in the *Toki–shakuyaku–san* group than in the oral iron group. In the *Toki–shakuyaku–san* group, intersubject and intrasubject variability of the serum ferritin level was noted, the MCHC increased significantly relative to the baseline value after 8 weeks of treatment, and the RBC and reticulocyte count also showed a tendency to increase. It was noteworthy that the PLT also increased significantly in this group, while the APTT decreased significantly and the PT showed a decreased tendency.

On the other hand, in the oral iron group, the RBC, Hb, Ht, MCV, MCH, MCHC, and serum ferritin level showed significant increase relative to the baseline values, however TIBC showed significant decrease and no significant change in the reticulocyte count

Table 2. The Variation of the Blood Test after the Drug Administration

Laboratory parameters	Drug	Baseline	At 4 weeks	At 8 weeks
RBC ($10^6/\mu l$)	*Toki-shakuyaku-san*	4.06±0.2	4.11±0.1	4.1±0.2
	Oral iron preparation	3.96±0.1	4.20±0.10	4.30±0.12*
Hb (g/dl)	*Toki-shakuyaku-san*	10.9±0.4	10.9±0.5	10.7±0.5 ‡
	Oral iron preparation	9.6±0.2	11.2±0.2*	12.1±0.2* ‡
Ht (%)	*Toki-shakuyaku-san*	33.0±1.2	33.2±1.4	32.2±1.4 ‡
	Oral iron preparation	29.8±0.6	34.0±0.5*	36.2±0.7* ‡
MCV (fl)	*Toki-shakuyaku-san*	79.5±1.8	78.3±1.9	78.0±2.3 ‡
	Oral iron preparation	75.4±1.4	81.3±1.4*	84.5±1.3* ‡
MCH (pg)	*Toki-shakuyaku-san*	26.1±0.7	25.7±0.8	26.0±0.8
	Oral iron preparation	24.4±0.6	26.8±0.6*	28.2±0.6*
MCHC (%)	*Toki-shakuyaku-san*	33.0±0.2	32.9±0.3	33.2±0.3*
	Oral iron preparation	32.3±0.2	32.9±0.2*	33.3±0.3*
Reticulocyte (%)	*Toki-shakuyaku-san*	11.4±1.5	11.8±1.9	13.3±1.1
	Oral iron preparation	13.5±1.2	19.4±1.4	12.1±1.6
PLT ($10^4/\mu l$)	*Toki-shakuyaku-san*	28.8±2.6	30.0±3.9	34.1±3.9*
	Oral iron preparation	31.8±1.8	27.8±1.9*	27.5±1.6*
PT (sec)	*Toki-shakuyaku-san*	10.9±0.1	11.0±0.2	10.5±0.2
	Oral iron preparation	11.0±0.2	10.5±0.2	10.8±0.2
APTT (sec)	*Toki-shakuyaku-san*	34.3±0.5	33.6±0.4	32.4±0.5* ‡
	Oral iron preparation	34.4±0.9	34.1±0.9	34.8±0.8 ‡
Fe (μg/dl)	*Toki-shakuyaku-san*	50±13 ‡	46±15 ‡	25±4 ‡
	Oral iron preparation	17±1 ‡	107±24* ‡	77±28* ‡
TIBC (μg/dl)	*Toki-shakuyaku-san*	413±23	422±19	429±16
	Oral iron preparation	423±25	367±25*	350±25*
Ferritine (ng/ml)	*Toki-shakuyaku-san*	5±1	12±9 ‡	3±0 ‡
	Oral iron preparation	3±0	9±1* ‡	6±1* ‡

Toki-shakuyaku-sangroup (n=10), Oral iron preparation group (n=13). Each values represents mean±S.E.
* Significantly different before and after the drug administration at $p<0.05$ by Wilcoxon's rank-sum test.
‡ Significantly different between *Toki-shakuyaku-san* and oral iron preparation at $p<0.05$ by Wilcoxon's signed-ranks test.

was observed. The serum Fe level increased significantly after 4 weeks (98±24 μg/dl) and 8 weeks (68±31 μg/dl) of the study treatment relative to the levels at baseline in analyzing it as changes. The PLT decreased significantly relative to the baseline count in this group, in contrast to the significant increase relative to the baseline count observed in the *Toki–shakuyaku–san* group, mentioned above.

Improvement of Signs and Symptoms The signs and symptoms were assessed at baseline, and after 4 and 8 weeks of the study treatment. Parameters which showed changes during the study period are shown in Table 3; higher scores indicate worse symptoms.

Concerning the symptoms of anemia, pallor, spoon shape of the nails, and dizziness on standing resolved significantly as compared to the baseline in the *Toki–shakuyaku–san* group. Soreness of the mouth and cracks at the angles, and shortness of breath also tended to improve in this group. In the oral iron group, improvement of the anemic condition was reflected by improvement in the laboratory parameters, as also by resolution of the pallor and spoon shape of the nails relative to the baseline. Dizziness on standing and shortness of breath also improved significantly after 8 weeks of treatment in this group. In regard to the symptoms of uterine myoma and symptoms associated with climacteric disturbances, such as menorrhagia, dysmenorrhea, cold feeling in the lower part of the body, cold hands and feet, dizziness, headache, and shoulder stiffness, significant improvement was noted after 8 weeks of treatment in the *Toki–shakuyaku–san* group; the bursts of sweating and tingling pain in the hands and

Table 3. Variability of Severity Scale for Subjective Findings after the Drug Administration

Clinical symptoms	Drug	N[a)]	Severity scale[b)]		
			Baseline	At 4 weeks	At 8 weeks
Pallor	*Toki-shakuyaku-san*	8	2.4±0.4	1.4±0.6*	1.3±0.4*
	Oral iron preparation	7	2.3±0.4	1.4±0.2	1.0±0.5
Spoon-shaped nails (koilonychias)	*Toki-shakuyaku-san*	7	2.0±0.2	1.5±0.5	0.8±0.2*
	Oral iron preparation	8	2.0±0.4	1.0±0.5	0.8±0.2
Dizziness on standing (lightheadedness)	*Toki-shakuyaku-san*	7	2.0±0.3	1.6±0.5	1.0±0.2*
	Oral iron preparation	9	1.6±0.2	1.0±0.2	0.5±0.3*
Soreness of the mouth and cracks at the angles	*Toki-shakuyaku-san*	2	1.5±0.5	1.0±0.0	0.0±0.0
	Oral iron preparation	6	0.8±0.2	1.2±0.4	0.8±0.3
Shortness of breath	*Toki-shakuyaku-san*	4	1.3±0.3	0.7±0.3	0.8±0.3
	Oral iron preparation	10	1.2±0.3	0.6±0.3	0.3±0.2*
Menorrhagia	*Toki-shakuyaku-san*	8	2.5±0.4	1.8±0.8	1.1±0.3*
	Oral iron preparation	12	2.5±0.4	2.2±0.4	2.1±0.4
Menstrual pain	*Toki-shakuyaku-san*	5	2.6±0.5	2.0±0.0	1.0±0.3*
	Oral iron preparation	9	2.0±0.3	1.7±0.5	1.9±0.4
Cold feeling in the lower part of the body	*Toki-shakuyaku-san*	6	1.3±0.2	0.8±0.3	0.3±0.2* ‡
	Oral iron preparation	5	1.2±0.7	2.5±0.9	2.0±0.6 ‡
Cold hands and feet	*Toki-shakuyaku-san*	7	1.7±0.3	1.3±0.5	0.7±0.2*
	Oral iron preparation	7	1.0±0.3	1.5±0.6	0.7±0.2
Dizziness	*Toki-shakuyaku-san*	6	1.8±0.3	1.0±0.6	0.8±0.4*
	Oral iron preparation	7	1.6±0.3	1.2±0.5	1.0±0.4
Headache	*Toki-shakuyaku-san*	6	1.7±0.2	0.8±0.3	0.5±0.2*
	Oral iron preparation	6	1.7±0.5	1.3±0.6	1.3±0.3
Shoulder stiffness	*Toki-shakuyaku-san*	8	1.5±0.3	1.0±0.0	0.4±0.2*
	Oral iron preparation	9	1.7±0.3	1.4±0.5	1.3±0.4
Bursts of sweating	*Toki-shakuyaku-san*	6	1.3±0.2	1.0±0.0	0.7±0.2
	Oral iron preparation	3	1.3±0.9	1.7±0.7	1.3±0.9
Tingling pain in the hands and feet	*Toki-shakuyaku-san*	4	1.3±0.3	0.7±0.3	0.3±0.3
	Oral iron preparation	7	0.7±0.3	0.8±0.3	0.4±0.2

a) N shows the patient number with the clinical symptom; *b*) Severity scale was calculated based on Table 1. Each values represents mean±S.E.
* Significantly different before and after the drugadministration at $p<0.05$ by Wilcoxon'srank-sum test.
‡ Significantly different between toki-shakuyaku-san and oral iron preparation at $p<0.05$ by Wilcoxon's signed-ranks test.

feet also tended to improve in this group. In contrast, no such remarkable improvement in subjective symptoms was observed in the oral iron group.

Side Effects During the interview by the pharmacist, the patients were asked about the occurrence of side effects during the study period. No side effects were encountered in the *Toki-shakuyaku-san* group, while 80.0% of patients in the oral iron group reported one or more side effects, including heartburn (46.7%), nausea (46.7%), vomiting (20.0%), diarrhea (20.0%), constipation (13.3%), abdominal distention (13.3%), anorexia (6.7%), and soft feces (6.7%) (Fig.1). Patients with abnormal findings were referred to a physician, and appropriate medical treatment was prescribed where necessary, including additional prescription of gastrointestinal drugs. In two patients, the oral iron supplement had to be stopped because of severe vomiting.

DISCUSSION

In this prospective study, we compared the efficacy and side effects of *Toki-shakuyaku-san* and an oral iron supplement in the treatment of anemia associated with menorrhagia attributable to uterine myoma, by assessing the improvement of signs and symptoms and laboratory biochemical parameters in these patient following either drug administration. Iron is needed for the production of hemoglobin. In the

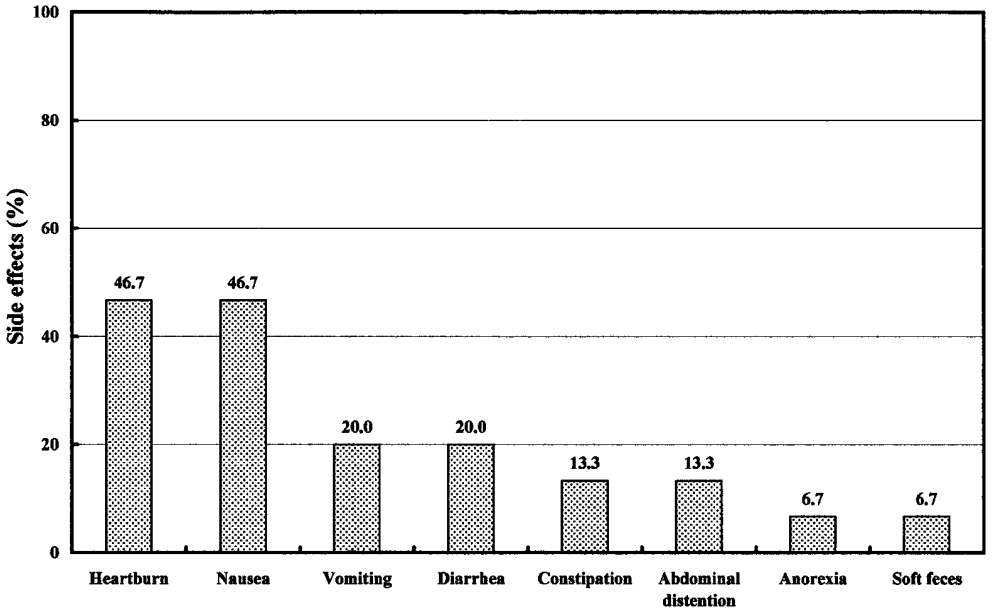

Fig. 1. Side Effects Encountered Following Administration of the Oral Iron Preparation to 15 Patients
This question is allowed to plural answers.

present study, oral iron supplementation improved the hematological and blood biochemical parameters, and also led to resolution of some signs and symptoms of anemia. However, gastrointestinal side effects were encountered in more than 80.0% of patients receiving the oral iron supplement, resulting in a poor medication compliance rate. In the *Toki–shakuyaku–san* group, while there was no significant improvement in the laboratory parameters reflective of the severity of anemia, marked resolution was noted of the symptoms and signs of anemia, such as pallor, koilonychia, and dizziness on standing, as also of those related to the uterine myoma, including menorrhagia and dysmenorrhea, and the climacteric symptoms of shoulder stiffness, dizziness, poor circulation, headache, etc without side effect. *Toki–shakuyaku–san* has been reported to be effective in the treatment of anemia of pregnancy.[5] Anemia of pregnancy is related to increase in the blood volume in normal pregnant women, when the increase in erythrocyte mass lags behind the increase in plasma volume, leading to blood dilution. This condition is sometimes called physiological anemia. *Toki–shakuyaku–san* has been known to improve anemia in pregnant women by facilitating water level control in body and hematopoiesis. The purpose of this study was to treat iron-deficiency anemia associated with menorrhagia attributable to uterine myoma. The water level control in body and hematopoietic effects of *Toki–shakuyaku–san* may not be useful for improving laboratory parameters in patients with anemia due to excessive menstrual bleeding. Another study has described that *Toki–shakuyaku–san* improved ovarian function, which led to the alleviation of excessive menstrual bleeding not related to uterine myoma.[10] Several investigators have referred to the effect of *Toki–shakuyaku–san* on menorrhagia, coagulation abnormalities and dysmenorrhea associated with uterine myoma. These findings suggest that *Toki–shakuyaku–san* may exert analgesic, spasmolytic, and hemostatic effects by controlling the adhesiveness of erythrocytes and preventing oxygen deficiency in tissues.[9]

Furthermore, in this study, the hemostatic effect of *Toki–shakuyaku–san* may also contribute to the alleviation of the symptoms of anemia, considering the observed relief of menorrhagia, increased platelet count, and reduction in APTT in the patients. No other study, however, has reported an increase in platelet count following the administration of *Toki–shakuyaku–san*. Further studies are required to clearly elucidate the mechanism of actions in *Toki–shakuyaku–san*. It might be considered that the relief of the subjective symptoms of climacteric disturbances is related to blood circulation, which suggests that the improvement of blood circulation in *Toki–*

shakuyaku–san as reported in experiments.[11]

Overall, in order to supply the iron of the anemia, it is considered that the iron preparation is useful. *Toki–shakuyaku–san* may be considered to be beneficial as an alternative medicine in the treatment of mild or moderate anemia associated with uterine myoma, when oral iron supplements as the first drugs of choice induce severe side effects. The use of this Kampo medicine could be expected to improve the patient's QOL by resolving the symptoms of anemia, menorrhagia, dysmenorrhea and climacteric disturbances in these cases.

Finally, combined therapy using *Toki–shakuyaku–san* with an oral supplement for anemia associated with uterine myoma may offer promise, since the same combination has been shown to be effective in the treatment of anemia of pregnancy.[12]

REFERENCES

1) Mizoguchi H., Yamada O., Urabe A., Takaku F., Kubota K., Miura Y., Iwata N., Maekawa T., *J. Ther.*, **66**, 161–168 (1984).
2) Terao T., Maki M., Suzuki M., *Obstet. Gynecol. Pract.*, **38**, 191–206 (1989).
3) Kato J., Kobune M., Kohgo Y., Sugawara N., Hisai H., Nakamura T., Sakamaki S., Sawada N., Niitsu Y., *J. Clin. Invest.*, **98**, 923–929 (1996).
4) Akase T., Mochizuki M., Sagawa K., Shimada S., Tashiro S., Tsuruta H., Nishijima M., *Rec. Prog. Kampo Med. Obstet. Gynecol.*, **13**, 62–65 (1996).
5) Tagawa K., Ogawa S., Kono M., Takagi S., *World Obstet. Gynecol.*, **31**, 66–73 (1979).
6) Terasawa K., ''Wakanshinryougaku,'' Igaku-Shoin, Tokyo, 1990, p. 253.
7) Aburada M., Akiyama Y., Ichio Y., Nakamura A., Ichikawa N., Pharmacometrics, 23, 981–997 (1982).
8) Mochizuki M., Kuwabara Y., ''Standard Textbook—Obstetrics and Gynecology,'' Igaku-Shoin, Tokyo, 1996, p. 107–113.
9) Kimura T., Tahara H., Uemura K., Gotoda Y., Araki H., *Kanagawa Dist. J. Jpn. Obstet. Gynecol. Soc.*, **25**, 33–36 (1989).
10) Inaba Y., Hori S., Hosoi N., Makino I., *Obstet. Gynecol. Pract.*, **33**, 767–778 (1984).
11) Toriizuka K., Zhang Tie Zhong, Terasawa K., Okamoto M., Tosa H., *J. Med. Pharm. Soc. WAKAN-YAKU*, **4**, 20–25 (1987).
12) Tagawa K., Ogawa S., Amemiya H., Takagi S., Kono M., *World Obstet. Gynecol.*, **33**, 47–51 (1981).