Efficacy of Rikkunshito, a Traditional Japanese Medicine (Kampo), in Treating Functional Dyspepsia

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Abstract

Background  Rikkunshito, a traditional Japanese (Kampo) medicine, is widely prescribed as an oral preparation for the treatment of functional dyspepsia (FD). In our previous study, we reported that extracorporeal ultrasonography (US) is a useful technique for the assessment of the gastric accommodation reflex (AR) and duodenogastric motility. In this study, we examined the effects of Rikkunshito on the gastroduodenal function in patients with FD.

Methods  Sixteen FD patients (median age, 45 y) underwent US, before and after 14 days of treatment with Rikkunshito (7.5 g b.d.). For assessment of the AR, a cross-sectional area of the proximal stomach was measured after incremental ingestion of a liquid meal up to 400-mL. The expansion rate was used as the parameter to determine the AR. Then, the gastric emptying rate (GER), motility index (MI), and reflux index (RI) were evaluated using previously reported methods.

Results  Although no significant changes were observed in the total score of the Gastrointestinal Symptom Rating Scale (GSRS), the scores of 3 of the 15 symptoms of GSRS decreased significantly after treatment with Rikkunshito. The expansion rate of the proximal stomach was significantly greater after treatment with Rikkunshito than before the treatment. Although the GER and MI increased significantly, no significant differences in the RI were observed after treatment with Rikkunshito.

Conclusion  These observations suggested that Rikkunshito may be beneficial for the treatment of FD patients with impaired AR and gastric motility. These results also suggested that Rikkunshito has a therapeutic potential for FD and GERD.

Key words: Rikkunshito, gastric accommodation reflex, gastroduodenal motility, ultrasound, traditional Japanese medicine (Kampo)

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Introduction

Functional dyspepsia (FD) is defined as the presence of gastrointestinal symptoms such as epigastric pain, epigastric burning, postprandial fullness, and early satiation in the absence of any organic, systemic, or metabolic disease.

On the basis of the Rome III criteria (1), FD is subdivided into 2 diagnostic categories: 1) meal-induced postprandial distress syndrome (PDS), which is characterized by postprandial fullness and early satiation, and 2) epigastric pain syndrome (EPS), which is characterized by epigastric pain and burning. These categories were proposed under the assumption that the 2 types of FD might arise from different underlying pathophysiological mechanisms. It has been suggested that impaired accommodation reflex...
(AR) of the proximal stomach and delayed gastric emptying may play major roles in the pathogenesis of the PDS subgroup (2). According to previous reports, these functional abnormalities are observed in 15% to 50% of all FD patients (3, 4). Therefore, assessment of both the gastric AR and gastroduodenal motility is essential for understanding the pathogenesis of FD.

Rikkunshito is an orally administered Japanese herbal (Kampo) preparation that is widely prescribed for patients showing various gastrointestinal symptoms such as gastroesophageal reflux (5, 6), dyspeptic symptoms of post gastrointestinal surgery (7, 8), and chemotherapy-induced nausea (9). Rikkunshito is composed of 8 constituents: Glycyrrhizae radix (4.7%), Zingiberis rhizoma (2.3%), Atractylodis lanceae rhizoma (18.6%), Zizyphi fructus (9.3%), Aurantii amomi pericarpium (9.3%), Ginseng radix (18.6%), Pinelliae rhizae radix (4.7%), and Hoelen (18.6%). Several studies have shown that many Japanese herbal medicines, including Rikkunshito, improve gastroduodenal motility-related disorders and are therefore clinically efficacious against FD to some extent (10-14). However, few studies have been reported on the action mechanism of this medicine in humans (15); although Rikkunshito has been demonstrated to improve the impairment in the gastric AR in vitro (16), no clinical reports have been published on the effects of Rikkunshito on the gastric AR.

In our previous study, we reported that extracorporeal ultrasonography (US) is a useful modality for the assessment of meal-induced gastric AR, gastric emptying rate (GER), antral contractions, and duodenogastric reflux (DGR) (17-22). The aim of this study was to determine the clinical effects of Rikkunshito on gastric AR and gastroduodenal motility in FD patients by using US.

**Subjects and Methods**

**Subjects**

Sixteen FD patients (10 men and 6 women; age range, 28-78 y; median age, 45 y) were enrolled in this study. All of the patients were diagnosed with FD according to the Rome III criteria. None of them had a history of diabetes mellitus and gastrointestinal surgery; they were not under any medications that could affect gastric motility. Smoking was prohibited on the day before and on both days of ultrasonographic examination. Candidates infected with *Helicobacter pylori* were not excluded from the study. The protocol for this study was approved by the Ethics Committee of Kawasaki Medical School, and all participants gave prior informed consent.

**Methods**

**Changes in gastrointestinal symptoms**

The changes in the gastrointestinal symptoms were evaluated on the basis of the Gastrointestinal Symptom Rating Scale (GSRS), Japanese edition (23). The GSRS is composed of 15 items, each rated according to severity on a scale of 1 (absence of the symptom) to 7 (maximal intensity of the symptom) (23); thus, higher GSRS scores indicate more severe symptoms. We used the total score and the 15 gastrointestinal symptoms of GSRS for evaluating the dyspeptic symptoms. The GSRS questionnaire was administered twice to each patient (before and after treatment with Rikkunshito).

**Assessment of AR**

The patients were examined by US, before and after 14 days of treatment with Rikkunshito (TJ-43; Tsumura, Tokyo, Japan) administered at a dose of 7.5 g b.d. The patients were asked to fast overnight and before the US examination, they were asked to consume incremental amounts of up to 400-mL of a liquid meal (consommé soup, 13 kcal/400-mL) through a straw. Thereafter, the cross-sectional area of the proximal stomach was measured for assessment of the gastric AR with the subjects lying on a bed in the supine position. In order to obtain the largest cross-sectional area of the proximal stomach, an US probe was positioned and maintained in the intercostal space of the left axilla (Fig. 1) of the patient, with the spleen as the landmark for this view (Fig. 2) as described previously (20-22). The cross-sectional area of the proximal stomach was estimated by tracing its mucosal side using built-in calipers for 1-2 minutes after the meal ingestion. The expansion rate in the cross-sectional area measured before and after treatment with the drug was expressed as follows: 

\[ \frac{\text{[area of each volume after ingestion} - \text{area before ingestion]} \times 100 \%] \]

**Assessment of gastroduodenal motility**

After the assessment of gastric AR, the patients were asked to sit on a chair, reclining slightly backwards, and the GER, antral contractions, and DGR were evaluated by US, as described previously (17-20, 22). The US probe was positioned vertically to simultaneously visualize the antrum, superior mesenteric artery, and abdominal aorta.

The antral area was estimated by tracing the mucosal side of the antrum with built-in caliper at 1 minute and 15 minutes after ingestion of the liquid meal. The GER was expressed as follows: 

\[ \frac{\text{[antral area at 1 minute} - \text{antral area at 15 minutes]} \times 100 \%] \]

The frequency of antral contractions was defined as the number of contractions per 3 minutes. The amplitude of the antral contractions was calculated from the maximal reduction in the antral area for each contraction as follows: 

\[ \frac{\text{[antral area at the time of relaxation} - \text{antral area at the time of contraction]} \times 100 \%] \]

The motility index (MI) was expressed as the product of the frequency of contractions and mean amplitude.

To evaluate the DGR by color Doppler US, we positioned the US probe at the level of the transpyloric plane to simultaneously visualize the antrum, pylorus, and proximal duodenum. The color gain, high-pass filter, and angle between
Figure 1. The position of the ultrasonography probe to obtain the largest cross-sectional area of the proximal stomach. The probe was placed in the intercostal space of the left axilla.

Figure 2. Changes in the US images of the largest cross-sectional area of the proximal stomach after incremental ingestion of up to 400-mL of a liquid meal. The incremental changes in the area of the proximal stomach positively corresponded to the intake volumes. The spleen was used as the marker for this view. The cross-sectional area of the proximal stomach was evaluated by marking the mucosal side with built-in calipers.

The US beam and the transpyloric flow were standardized for all measurements. The frequency of DGR was defined as the amount of DGR obtained at a distance “x” (measured in cm) of the color signal from the pylorus. The reflux index (RI) was expressed as follows: “frequency of DGR × mean intensity of DGR.”

All of the evaluations were performed by one researcher (Kusunoki H). The equipment used was an SSA-770A US system (Toshiba, Nasu, Japan) with a 3.75-MHz curved array scanner.

Statistical analysis

The data are expressed as mean ± SE. The statistical significance of differences between the 2 groups was assessed.
using the Mann-Whitney’s test, the Wilcoxon test, or the Student’s t-test. The difference was considered statistically significant if \( p<0.05 \).

**Results**

**Changes in gastrointestinal symptoms**

Although the total score of GSRS decreased after treatment with Rikkunshito, the differences were not statistically significant (Fig. 3). However, the scores of 3 of the gastrointestinal symptoms of GSRS (abdominal pain, heartburn, and abdominal distension) decreased significantly after treatment with Rikkunshito (Table 1).

**Assessment of AR**

The expansion rate in the cross-sectional area of the proximal stomach was significantly greater after treatment with Rikkunshito than before the treatment (before treatment vs. after treatment: after 100-mL ingestion, 2.20±0.28 vs. 3.27±0.45, \( p=0.034 \); after 200-mL ingestion, 3.69±0.57 vs. 6.51±1.39, \( p=0.007 \); after 300-mL ingestion, 5.13±0.97 vs. 9.08±2.06, \( p=0.017 \); and after 400-mL ingestion, 6.40±1.29 vs. 11.29±2.48, \( p=0.017 \) (Fig. 4).

**Assessment of gastroduodenal motility**

Although the values of GER [before treatment vs. after treatment: 57.9±5.7 vs. 72.3±5.4, \( p=0.010 \)] and MI [7.93±0.48 vs. 8.88±0.24, \( p=0.049 \)] increased significantly after Rikkunshito treatment, those of RI [18.8±3.1 vs. 15.3±3.0, \( p=0.463 \)] were not significantly different (Fig. 5). None of the subjects had any adverse events that necessitated withdrawal from the study.

**Table 1.** Changes in the 15 Items of Gastrointestinal Symptoms of GSRS were Shown in the Table1. The Scores of Three Items of Gastrointestinal Symptoms (Abdominal Pains, Heartburn, and Abdominal Distension) of GSRS Decreased Significantly after Treatment with Rikkunshito.

<table>
<thead>
<tr>
<th>Symptoms of GSRS</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pains</td>
<td>3.06±0.47</td>
<td>1.88±0.30</td>
<td>0.008</td>
</tr>
<tr>
<td>Heartburn</td>
<td>2.31±0.35</td>
<td>1.50±0.26</td>
<td>0.024</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>2.31±0.34</td>
<td>2.00±0.32</td>
<td>NS</td>
</tr>
<tr>
<td>Sucking sensation in the epigastrium</td>
<td>1.88±0.22</td>
<td>1.81±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2.31±0.50</td>
<td>1.63±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Borborygmus</td>
<td>2.06±0.35</td>
<td>1.56±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2.19±0.29</td>
<td>1.50±0.52</td>
<td>0.028</td>
</tr>
<tr>
<td>Ercutation</td>
<td>2.13±0.27</td>
<td>1.88±0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Increased flatus</td>
<td>2.31±0.44</td>
<td>2.38±0.40</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased passage of stools</td>
<td>2.31±0.42</td>
<td>1.94±0.36</td>
<td>NS</td>
</tr>
<tr>
<td>Increased passage of stools</td>
<td>1.81±0.37</td>
<td>1.44±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>Loose stools</td>
<td>1.81±0.33</td>
<td>1.44±0.22</td>
<td>NS</td>
</tr>
<tr>
<td>Hard stools</td>
<td>1.88±0.29</td>
<td>1.88±0.35</td>
<td>NS</td>
</tr>
<tr>
<td>Urgent need for defeication</td>
<td>1.38±0.26</td>
<td>1.38±0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>2.13±0.30</td>
<td>1.88±0.26</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 4. The expansion rate in the cross-sectional area measured before and after treatment with Rikkunshito was expressed as 

\[
\text{Expansion Rate} = \left( \frac{\text{area of each volume after ingestion} - \text{area of each volume before ingestion}}{\text{area before ingestion}} \right) \times 100 \%
\]

The expansion rate in the cross-sectional area of the proximal stomach was significantly greater after treatment with Rikkunshito than before the treatment.

Figure 5. Changes in the gastric emptying rate (GER), motility index (MI), and reflux index (RI) before and after treatment with Rikkunshito. Although the values of GER and MI increased significantly after Rikkunshito treatment, those of RI were not significantly different.
Discussion

Traditional Japanese (Kampo) medicines are widely prescribed in Japan for patients with various gastrointestinal symptoms, and Rikkunshito is the most popular Kampo medicine prescribed for the treatment of FD. Some clinical studies have reported that Rikkunshito is efficacious in the treatment of FD-related gastrointestinal symptoms and has been used in several studies (4, 25, 30-33). However, this method is invasive and because the presence of food in the stomach would interfere with the expansion of the balloon of the barostat system, the value of the postprandial gastric volume may be less than that recorded before consuming the test meal (34). Similarly, the US method has the same disadvantage as the barostat, i.e., it requires the patients to be in the supine position for partial distribution of the liquid test meal in the proximal stomach. Therefore, the US method also cannot be used to evaluate the AR with normal gastric distribution of a liquid test meal. However, we selected the US method for easy AR assessment.

Rikkunshito has reported improvement in delayed gastric emptying in rats in vivo (35). However, there are few reports discussing the clinical effects of Rikkunshito on gastroduodenal motility in humans (19). In a previous study by Tatsuta and Ishii, 42 patients with FD were randomly divided into the “Rikkunshito-treated” group and the “Combizym-treated” group; they reported that Rikkunshito enhances gastric emptying and provides significantly greater relief from some symptoms than Combizym (11). In their recent study, Kawahara et al demonstrated that administration of Rikkunshito results in symptomatic relief and improves gastric emptying in patients with severe FD because of delayed gastric emptying (6). In the present study, we showed that Rikkunshito administration enhanced the meal-induced AR of the proximal stomach, GER, and MI in patients with FD. Therefore, our results were consistent with the reports of previous studies indicating that this drug has an effect on gastric motility.

With regard to the role of Rikkunshito in the enhancement of AR, GER, and MI, the precise mechanisms underlying the effects of Rikkunshito on gastric AR and gastroduodenal motility are still unclear; however, the pharmacological mechanisms and active ingredients of Rikkunshito have been elucidated in part (16, 35). Factors associated with gastric motility, such as gastric emptying and gastric AR, are regulated by various effectors, including nitric oxide (NO), 5-hydroxytryptamine (5-HT), and its receptors. Studies have shown that the prokinetic actions of Rikkunshito are mediated by NO (16, 35, 36). Initially, the actions of Rikkun-
shito were thought to be mediated via NO production alone because it contains L-arginine, a substrate of NO, in its water fraction. Subsequently, analysis of the fractional extracts of Rikkunshito revealed that the methanol fraction contained an even more potent promoter of gastric motility, namely, hesperidin (35). It was reported that hesperidin is not a substrate of NO because it does not belong to the guanidine group (37) and that it actually decreases NO production (38). Thus, Rikkunshito and hesperidin were believed to promote gastric motility through a mechanism other than that mediated by NO. However, in a recent study, Tominaga et al (39) reported that Rikkunshito has no effect on dopamine-induced gastrointestinal motility. They also reported that Rikkunshito has 5-HT3-antagonist effects on gastric motility. Initially, we believed that the role of Rikkunshito in promoting gastric motility may be mediated by ghrelin because Rikkunshito elevates the low plasma ghrelin levels that are induced by cisplatin (40). Some subsequent studies (41-43) revealed that the pharmacological actions of Rikkunshito in promoting gastric motility may be associated with ghrelin. Therefore, our results corroborate the evidence obtained by previous studies showing that Rikkunshito has an effect on gastric motility.

In the present study, although we confirmed the gastric prokinetic actions of Rikkunshito by US evaluation, Rikkunshito did not show any significant effect on DGR. The DGR occurs as a result of the reversal of the original pressure gradient between the duodenum and the antrum. The mechanism underlying this phenomenon is unclear; the DGR may be related to a duodenal brake caused by early gastric emptying. Thus, a decrease in DGR reflects the normalization of gastrointestinal coordination.

In summary, this study showed that Rikkunshito enhanced meal-induced gastric AR, GER, and MI in patients with FD and that the scores of three of the gastrointestinal symptoms of GSRS (abdominal pain, heartburn, and abdominal distension) decreased significantly after treatment with Rikkunshito. These observations suggested that Rikkunshito may be beneficial for the treatment of FD patients with impaired AR and gastric motility. These results also suggested that Rikkunshito has a therapeutic potential for FD (both PDS and EPS) and GERD.

References