

# Effects of the Addition of Mosapride to Gastroesophageal Reflux Disease Patients on Proton Pump Inhibitor: A Prospective Randomized, Double-blind Study

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## Background/Aims

Proton pump inhibitors (PPIs) which are the most effective agents for the treatment of gastroesophageal reflux disease (GERD), have been known to delay gastric emptying. Mosapride has been used as prokinetics by accelerating gastric emptying. We evaluated the efficacy of mosapride to prevent PPI-induced delayed gastric emptying in a prospective randomized, double-blind and placebo-controlled trial.

## Methods

Thirty patients who were diagnosed as GERD and had normal gastric emptying were included in this study. PPI monotherapy group was treated with placebo drug in addition to pantoprazole and PPI plus mosapride group was treated with mosapride in addition to pantoprazole for 8 weeks. Gastric emptying scan and questionnaires about GERD and dyspeptic symptoms were assessed by scoring before and after treatment. To evaluate the changes of gastrointestinal endocrine hormones by PPI which are associated gastric acid secretion and gastric motility, fasting plasma gastrin and cholecystokinin were taken at weeks 0 and 8.

## Results

Half gastric emptying time was increased ( $P = 0.023$ ) in PPI monotherapy group, and there were no significant changes in PPI plus mosapride group. Plasma gastrin level increased in PPI monotherapy group ( $P = 0.028$ ) and there were no significant changes in PPI plus mosapride group. Plasma cholecystokinin level was not changed after treatment in both groups. GERD symptoms were improved after treatment in both groups, and postprandial bloating and nausea were improved in PPI plus mosapride group.

## Conclusions

Mosapride showed to be effective in preventing delayed gastric emptying and the increase in plasma gastrin level induced by PPI treatment, but did not show prominent clinical symptom improvements.

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## Key Words

Gastric emptying; Gastroesophageal reflux; Mosapride; Proton pump inhibitors

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Conflicts of interest: None.

Author contributions: Hyun Chul Lim analyzed data and wrote the manuscript. Hyojin Park designed organized and mediated the present study and supervised the manuscript. Jie-Hyun Kim, Young Hoon Youn, Eun Hee Lee and Byung Keon Lee revised the manuscript and advised design of study.

## Introduction

Gastroesophageal reflux disease (GERD) is one of the most common disease characterized by reflux symptoms like heartburn and acid regurgitation.<sup>1,2</sup> The treatment of GERD is based on anti-secretory compounds, including histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) and proton pump inhibitors (PPIs).<sup>3</sup> PPIs are widely used due to providing more long-lasting symptom relief with esophageal healing than any other available drugs including H<sub>2</sub>RAs, currently.<sup>4</sup>

However, PPIs have been known to delay gastric emptying from 15% to 40%.<sup>5-7</sup> The mechanisms for delayed gastric emptying induced by PPIs were discussed as decreased gastric acid which resulted in inadequate hydrolysis of food, enhanced secretion of gastrin, and decreased fluid secretion into the stomach.<sup>6,8,9</sup> Delayed gastric emptying could influence functional gastrointestinal disorders including gastroesophageal reflux disease, peptic ulcer disease and functional dyspepsia.<sup>10-12</sup>

Mosapride is a selective 5-hydroxytryptamine type 4 (5-HT<sub>4</sub>) receptor agonist and has been used in patients with upper gastrointestinal disorders by shortening gastric emptying in healthy volunteers and gastroparesis.<sup>13,14</sup>

Gastrin and cholecystokinin (CCK) are homologous gastrointestinal endocrine hormones which are known to regulate gastric acid secretion, gastric emptying, growth of gastric mucosa and intestinal motility in upper gastrointestinal tract.<sup>15-17</sup>

We conducted a prospective randomized, double blind and placebo-controlled clinical trial to evaluate the hypothesis that mosapride can normalize or prevent PPI-induced delayed gastric emptying, and we evaluated the changes of gastrointestinal endo-

crine hormones and upper gastrointestinal symptoms between PPI monotherapy group and PPI plus mosapride group.

## Materials and Methods

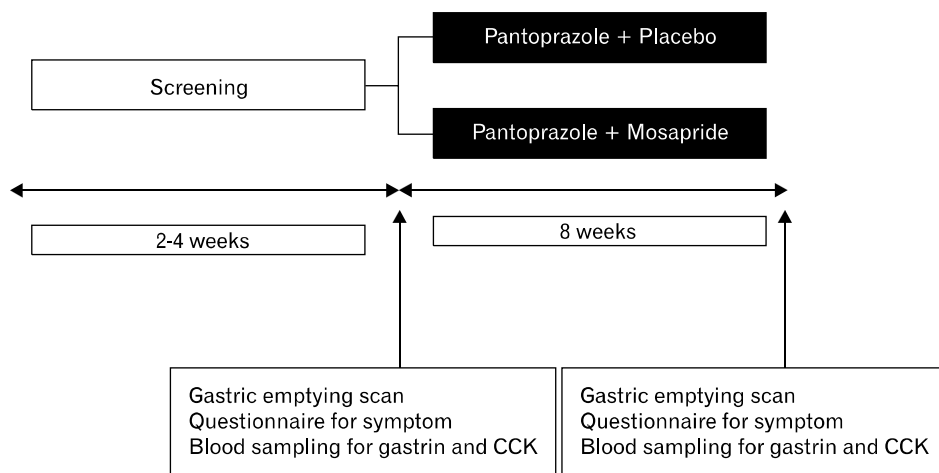
### Setting and Participants

Patients were recruited from the Gangnam Severance Hospital, Yonsei University, Korea, between September 2008 and June 2010. The study was conducted in accordance with the Declaration of Helsinki and this study protocol was approved by the Yonsei University College of Medicine Ethics Committee. Written informed consents were obtained from all patients prior to participation. The patients who were diagnosed as GERD by applying the Montreal criteria and had normal gastric emptying were included.<sup>18</sup> Exclusion criteria included patients (1) who had organic gastrointestinal disease including inflammatory bowel disease, cancer and ulcer (2) who took drugs which could affect evaluation of the treatment; other PPIs, H<sub>2</sub>RAs, prokinetics, mucosal protective agents, antacids, cholinergic and anticholinergic agents, and antidepressants for at least 4 weeks prior to study start, (3) who had severe systemic diseases including hepatic and nephrotic disease, (4) who had previous gastrectomy history, and (5) who was in state of pregnancy.

### Study Design and Treatment Protocol

#### Medication protocol

Patients in PPI monotherapy group were given pantoprazole 40 mg once daily (<sup>®</sup>Pantoloc; Pacific Pharma Co. Ltd., Seoul, Korea) and placebo tablets that were identical to mosapride citrate tablets t.i.d (3 times a day) (Daewoong Pharm Co. Ltd.,



**Figure 1.** Study flow diagram. CCK, cholecystokinin.

Seoul, Korea) for 8 weeks. Patients in PPI plus mosapride group were given pantoprazole 40 mg once daily and mosapride citrate (<sup>®</sup>Gasmotin; Daewoong Pharma Co. Ltd., Seoul, Korea), 5 mg t.i.d for 8 weeks. The drugs which could affect the gastrointestinal function and gastric acid secretion were not allowed to be used throughout the study.

### Visit Schedule and Outcome Assessments (Fig. 1)

This study was conducted as a prospective randomized, double-blind, placebo-controlled study. After informed consent was obtained, the screening examinations were conducted including a complete medical history, esophagogastroduodenoscopy, and blood sampling. Patients recorded questionnaires regarding gastroesophageal reflux symptoms including heartburn, acid regurgitation and dyspeptic symptoms including nausea/vomiting, belching, postprandial fullness, postprandial bloating and early satiety. The symptom severity was assessed with response options as no symptom (0), mild (1), moderate (2) or severe (3). Patients who were determined to meet all inclusion/exclusion criteria were randomized into 2 study group by PPI monotherapy group and PPI plus mosapride group, and underwent the first gastric emptying study and serum test for fasting plasma gastrin and plasma CCK.

After 8 weeks of drug treatment, all subjects visited hospital for a second gastric emptying study. Symptom scores were checked by questionnaires about gastroesophageal reflux symptoms, dyspeptic symptoms and any reported adverse events were checked in this visit. The patients who consented blood samplings were checked on the plasma gastrin and plasma CCK.

### Quantification of Gastric Emptying

Gastric emptying scan was assessed by a standardized scintigraphy method.<sup>19,20</sup> After a 12 hour fast, patients underwent scintigraphy after ingestion of the standard solid meal in the sitting position. The solid meal was consisted of 50 g of scrambled eggs (75 kcal) and 210 g of boiled rice (315 kcal, Korean standard diet) which was labeled with 500  $\mu$ Ci of <sup>99m</sup>Tc-pertechnetate. The contents of the radioactive materials in the stomach were measured by external scintigraphy using a gamma camera with a low-energy, all-purpose, parallel-hole collimator, immediately following completion of meal and then at 30, 60 and 90 minutes after the end of meal. The main parameters were half gastric emptying time ( $T_{1/2}$ , minutes) and percentage of gastric retention at 30, 60 and 90 minutes.  $T_{1/2}$  was defined as the time taken to

empty 50% of the gastric content.

### Plasma Gastrin and Cholecystokinin

Whole blood samples (5 mL) were collected from patients after fasting for 12 hours. Blood samples were immediately centrifuged and then stored at -20°C until the assay. Plasma gastrin-17 level was determined by using enzyme immunoassays kit (Biohit Plc., Helsinki, Finland) and plasma CCK level was measured with enzyme immunoassays kit (Phoenix Pharmaceuticals, CA, USA) with range of 0-100 ng/mL.

### Statistical Methods

Demographic characteristics and individual symptom scores from baseline and follow-up visit were compared between PPI monotherapy group and PPI plus mosapride group by the student's *t* test, or by the nonparametric Mann-Whitney U test if required. In addition,  $T_{1/2}$  and residual gastric contents at 30, 60 and 90 minutes calculated by gastric emptying scan and fasting plasma gastrin (pg/mL) and CCK (ng/mL) level from baseline and follow-up visit were compared between PPI monotherapy group and PPI plus mosapride group by the student's *t* test. Data are presented as mean  $\pm$  standard error and all efficacy analyses were based on two-sided tests, with  $P \leq 0.05$  considered as significant. All analyses were performed using SPSS 12.0 (SPSS Inc., Cary, NC, USA).

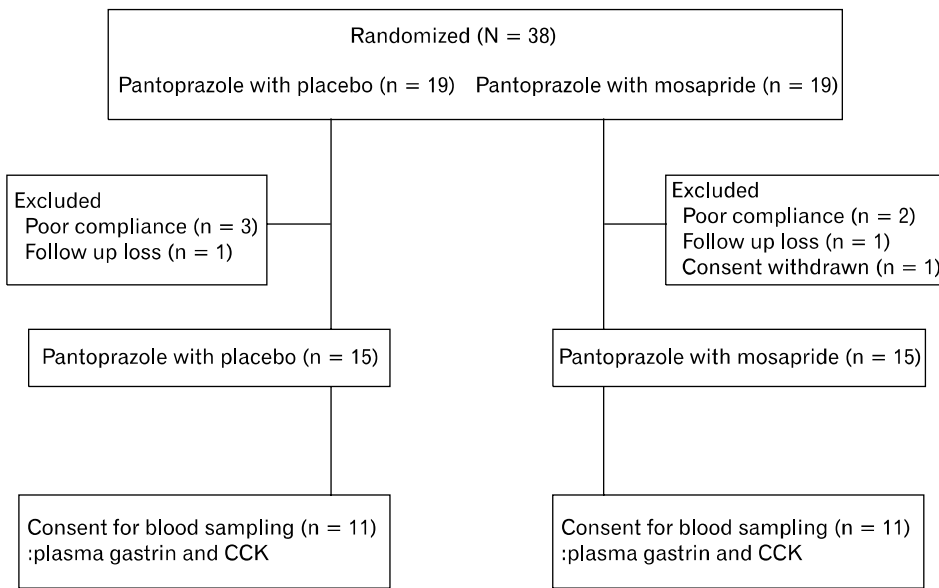
## Results

### Participant Flow and Follow-up

Thirty-eight patients screened (mean age 50.8 years [range 20-70]; 19 males, 19 females) were randomized into the study either as PPI monotherapy group or PPI plus mosapride group in accordance with the study design (Fig. 2). Eight patients discontinued the study, and there were no statistical differences in demographic characteristics between both groups (Table).

### Gastric Emptying Scan

Results of gastric emptying between pre-treatment vs post-treatment are presented in Figure 3. PPI monotherapy significantly delayed gastric emptying increasing  $T_{1/2}$  from  $57.5 \pm 12.9$  minutes to  $88.5 \pm 48.2$  minutes ( $P = 0.023$ ). The concomitant use of PPI and mosapride, showed no significant changes in gastric emptying;  $T_{1/2}$  from  $61.2 \pm 17.8$  minutes to  $65.0 \pm 15.5$  minutes ( $P = 0.536$ ).

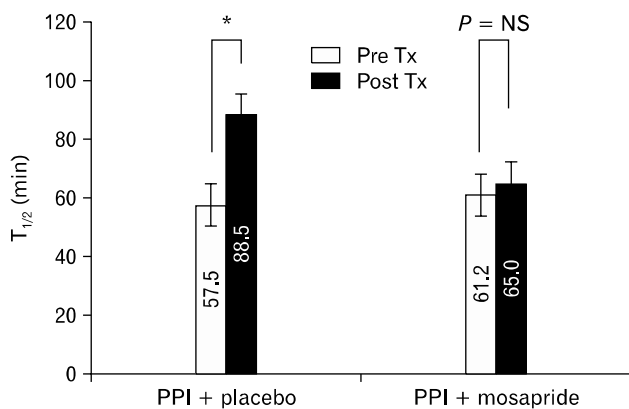


**Figure 2.** Flowchart of patient management in the study. CCK, cholecystokinin.

**Table.** Demographic Characteristics by Treatment Group

	PPI group (n = 15)	PPI + mosapride group (n = 15)	P-value
Age (mean age [range], yr)	53.27 (25-66)	48.47 (20-70)	0.302
Sex (M:F)	10:5	6:9	0.153
Height (mean ± SE)	166.7 ± 6.5	163.7 ± 9.7	0.328
Weight (mean ± SE)	65.9 ± 10.2	62.2 ± 12.9	0.404

PPI, proton pump inhibitor.



**Figure 3.** Effect of proton pump inhibitor (PPI) plus placebo drugs (n = 15) and PPI plus mosapride (n = 15) for 8 weeks on time to gastric half-emptying ( $T_{1/2}$ ) (mean ± SEM). \* $P < 0.05$ .

When examined sequentially over time, PPI increased gastric retention (i.e., delayed gastric emptying) by  $12.1 \pm 7.9\%$  ( $P = 0.006$ ) at 30 minutes,  $17.9 \pm 7.6\%$  ( $P = 0.005$ ) at 60 minutes, and  $19.5 \pm 8.0\%$  ( $P = 0.006$ ) at 90 minutes when compared

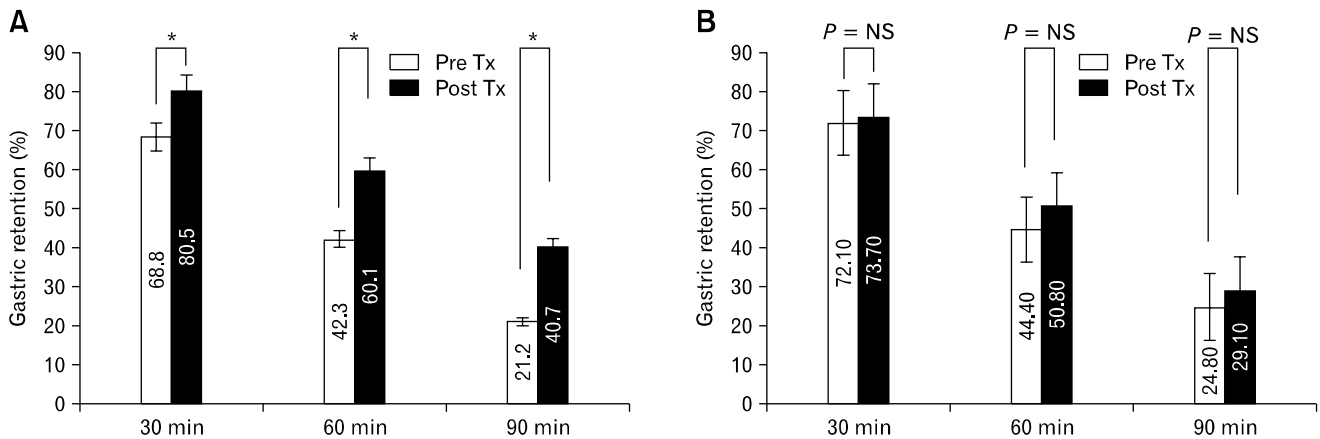
with baseline (Fig. 4A). In contrast, in the group receiving PPI plus mosapride, gastric retention was not changed at 30, 60 and 90 minutes compared with baseline (Fig. 4B).

### Fasting Plasma Gastrin and Cholecystokinin

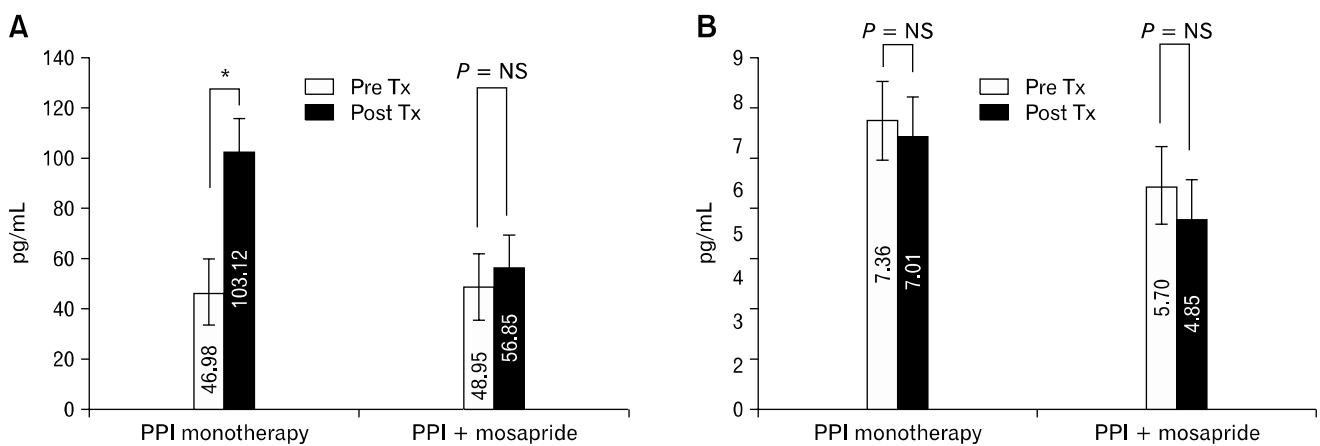
Plasma gastrin levels were within normal range ( $< 50$  pg/mL) in both groups at baseline, but showed significantly higher level in PPI monotherapy group after treatment end points ( $46.58$  pg/mL vs.  $103.11$  pg/mL,  $P = 0.028$ ) (Fig. 5A). Plasma CCK was within normal range in baseline and there were no significant changes after treatment in both groups (Fig. 5B).

### Clinical Efficacy Parameters

Gastrosophageal reflux symptoms were improved after treatment and there were no significant differences between 2 groups (Fig. 6). In the aspect of dyspeptic symptom, belching and postprandial fullness were improved in PPI monotherapy group. Nausea/vomiting and postprandial bloating additional to belching and postprandial fullness were improved in PPI plus mo-



**Figure 4.** (A) Effect of proton pump inhibitor (PPI) plus placebo drugs ( $n = 15$ ) for 8 weeks on percentage of gastric retention at 30, 60 and 90 minutes after test meal (mean  $\pm$  SEM) and (B) PPI plus mosapride ( $n = 15$ ) for 8 weeks on percentage of gastric retention at 30, 60 and 90 minutes after test meal (mean  $\pm$  SEM.). \* $P < 0.05$ .



**Figure 5.** (A) Changes in fasting plasma gastrin level between proton pump inhibitor (PPI) + placebo group ( $n = 11$ ) and PPI + mosapride group ( $n = 11$ ) before and after treatment (B) Changes in fasting cholecystokinin gastrin level between PPI + placebo group ( $n = 11$ ) and PPI + mosapride group ( $n = 11$ ) before and after treatment. \* $P < 0.05$ .

sapride group. Early satiety did not show significant change after treatment in both groups (Fig. 7).

## Adverse Events

Neither group of volunteers reported any severe side effects or clinically significant adverse events after randomization and during drug treatment. All adverse events were mild. In PPI monotherapy group, abdominal bloating (1 occurrence) and vomiting (1 occurrence) were noted, and in PPI plus mosapride group, vomiting (2 occurrences) and abdominal pain (1 occurrence) were reported.

## Discussion

The main treatment for GERD is potent acid suppression by using PPI.<sup>21,22</sup> Adding prokinetic drugs to PPI in the treatment of GERD is recommended, due to enhancing esophageal motor function, although the efficacy is controversial.<sup>23-27</sup> PPI induced the delay of gastric emptying in solid food, but there was few literature about prevention of the treatment delayed gastric emptying, and evaluations on dyspeptic symptoms.<sup>8,28-30</sup> Tegaserod (5-HT<sub>4</sub> receptor agonist) was used to normalize the delayed gastric emptying caused by PPIs in previous study, but tegaserod is out of market from its cardiovascular risk, so there is no proven safe

drug which was studied for preventing the PPI induce delayed gastric emptying.

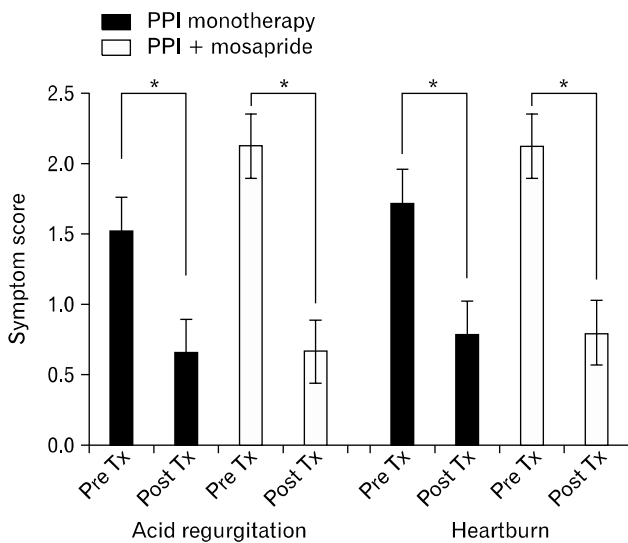
In present study, the efficacy of mosapride citrate for preventing the PPI induced gastric emptying was assessed. Mosapride citrate, a 5-HT<sub>4</sub> receptor agonist, is a prokinetic drug used in functional gastrointestinal disorder including gastroesophageal reflux disease and functional dyspepsia and is safe for it does not cause QT prolongation.<sup>31,32</sup> The action mechanism of mosapride includes enhancement of esophageal motor function, acceleration

of gastric emptying, and enhanced acid inhibitory effect of PPIs in humans.<sup>23,33-35</sup>

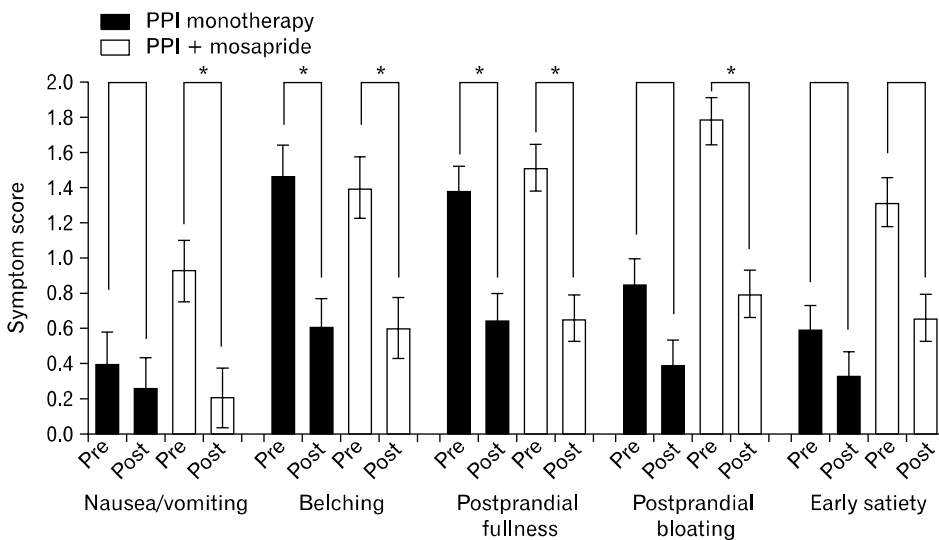
In this study, PPI treatment was associated with significant delays in gastric emptying by 53.9% prolongation in T<sub>1/2</sub> compared to baseline which was slightly higher than the previous report with 15-40% delay in T<sub>1/2</sub> during PPI treatment.<sup>5,36</sup> However, with mosapride added to PPI, the delayed gastric emptying did not occur. The delaying effect of PPI on gastric emptying appears to be manifested by the increase in percentage of meal retained at 30, 60 and 90 minutes compared with pre-treatment baseline values. The observation in this study is that mosapride effectively prevented the delay in gastric emptying induced by PPI as by the prokinetic effect.

In aspect of gastrointestinal endocrine hormones, plasma gastrin level was increased in PPI monotherapy group as is known,<sup>15</sup> but there was no significant change in PPI plus mosapride group after treatment. The mechanism for the normalization of gastrin level in PPI plus mosapride group could be as follows: emptying of solid food contents in the stomach increases by mosapride and less acid secretion for hydrolysis is needed compared to PPI monotherapy. Lowered needs for the acid secretion could inhibit the increase in the plasma gastrin level and consequently G-cell hyperplasia by the feedback mechanism. Although more study in gut hormone changes by prokinetic drug is needed, PPI plus mosapride therapy could prevent the dyspeptic symptom development after discontinuation of PPI by inhibiting increased serum gastrin level and G cell hyperplasia.

CCK is known to be associated with decrease of antral motility and previous studies showed that PPI induced the decrease



**Figure 6.** Changes in gastroesophageal reflux symptoms (acid regurgitation and heartburn) between the proton pump inhibitor (PPI) + placebo group (n = 15) and the PPI + mosapride group (n = 15) before and after treatment. \*P < 0.05.



**Figure 7.** Changes in dyspeptic symptoms (nausea/vomiting, belching, postprandial fullness, postprandial bloating and early satiety) between the proton pump inhibitor (PPI) + placebo group (n = 15) and the PPI + mosapride group (n = 15). \*P < 0.05.

of plasma CCK, but in our study there was no significant change in plasma CCK level after treatment.<sup>37,38</sup> In addition to the fasting state in this study, complementary measurements of the postprandial CCK level would be needed to clarify the relationship between gastrointestinal symptom and plasma CCK level.

In the aspect of association of the endocrine hormone changes and delayed gastric emptying after PPI therapy, plasma gastrin is more related to regulation of gastrointestinal motility rather than plasma CCK.

In symptomatic aspects, reflux symptoms including heartburn and acid regurgitation were improved both in PPI monotherapy and PPI plus mosapride group, and there were no significant difference between both groups, as reported in previous studies.<sup>32</sup> In dyspeptic symptoms, belching and postprandial fullness were improved in both group, but nausea and postprandial bloating symptoms were improved in PPI plus mosapride group. This could be an evidence that mosapride improved dyspeptic symptoms by additional gastroprokinetic effect, but this study had a limitation because baseline symptom scores before treatment in PPI plus mosapride group was higher than PPI monotherapy. The early satiety symptom was not improved in both groups, and it could be partially explained by the unchanged CCK level which shows the control of food intake.<sup>39</sup> Reason for the mismatching of gastric emptying and dyspeptic symptoms is that functional dyspepsia is multifactorial pathogenesis, which includes delayed gastric emptying, impaired gastric accommodation of food intake, and hypersensitivity to gastric distention.

In summary, we found that mosapride combination therapy to PPIs prevent PPI-induced delayed gastric emptying and increased plasma gastrin level, and there were mild improvements of dyspeptic symptoms. There are several limitations in our study, resulting from factors such as the small number and the characteristics of subjects (i.e., sex difference) due to dropped-out. Although larger-scale trial is needed to validate the clear benefit of mosapride in the clinical symptom improvements by preventing delayed gastric motility when using PPIs, data in this study provide evidence that PPIs plus mosapride combination therapy in GERD is able to prevent dyspeptic symptoms induced by the long-term maintenance treatment or after the discontinuation of PPIs therapy.

## Acknowledgements

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