

## Analyses of the Efficacy of Adjunctive Mosapride Citrate with Polyethylene Glycol Solution for Bowel Preparation for Colonoscopy Using Salivary Stress Markers

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### ABSTRACT

**AIM:** The efficacy and safety of adjunctive mosapride citrate with polyethylene glycol (PEG)-electrolyte solution for bowel preparation before colonoscopy have been reported. However, the effects of adjunctive mosapride citrate on the improvement of the participant's stress were not fully understood.

**METHODS:** This was a randomized, prospective, open-label study of mosapride in addition to PEG solution. A participant received one of two regimens in bowel preparation for colonoscopy [1 500 mL PEG plus mosapride citrate (mosapride group) or 2 000 mL PEG alone (control group)]. The bowel preparation status was compared between the two groups. Patients completed a questionnaire reporting the tolerability of the bowel preparation process. Salivary alpha-amylase (SAA) was measured as a stress marker at 0, 30, 60, and 120 min of the bowel preparation.

**RESULTS:** The bowel preparation status of the mosapride group was significantly better than that of the control group ( $P < 0.05$ ). There were no problematic adverse events in either group. A visual analogue scale (VAS) of the discomfort assessment was significantly better in the mosapride group ( $P < 0.05$ ). The frequency of patients that complained of nausea was significantly lower in the mosapride group ( $P < 0.05$ ). Salivary alpha-amylase increased with consumption of PEG, which means bowel preparation with PEG solution is stressful for participants. However, there were no differences in the SAA levels between the mosapride and control groups.

**CONCLUSIONS:** Mosapride citrate was an effective and safe adjunct to PEG solution for bowel preparation. A salivary stress marker demonstrated that bowel preparation was stressful for participants. The VAS score was more sensitive than the SAA for showing the differences between the mosapride and control groups.

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**Key words:** Mosapride citrate; Bowel preparation; Polyethylene glycol-electrolyte solution; Colonoscopy; Stress; Salivary alpha-amylase

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### INTRODUCTION

Adequate bowel preparation is required for safe and effective colonoscopy<sup>[1,2]</sup>. Inadequate preparation not only decreases the sensitivity of colonoscopic examination, but also increases the risk of complications<sup>[1,2]</sup>. Polyethylene glycol (PEG)-electrolyte solution is useful for good bowel cleansing and is used worldwide. However, patients needed to take approximately 2 000 mL of PEG solution orally for adequate bowel preparation<sup>[3]</sup>. The need to drink such large volumes of liquid with an unpalatable taste has a negative impact on patient compliance<sup>[4]</sup>. Therefore, more effective and tolerable bowel preparation regimens for colonoscopy are required to improve the acceptability of colonoscopy. Prokinetics such as domperidone, metoclopramide, and cisapride have been used in combination with PEG solution to improve the quality of bowel preparation<sup>[5,6]</sup>.

Some clinical studies have reported that mosapride citrate (mosapride) in combination with PEG may enhance bowel cleansing and improve patient acceptability and tolerability<sup>[7-9]</sup>. Mosapride is a selective 5-hydroxy-tryptamine-4 (5-HT<sub>4</sub>) receptor agonist and enhances gastric emptying and motility by facilitating acetylcholine release from the enteric cholinergic neurons<sup>[10]</sup>. There are 5-HT<sub>4</sub> receptors located in the human colon and rectum<sup>[11]</sup>, thus it seems to be reasonable to use adjunctive mosapride with PEG solution for

bowel preparation to improve patient acceptability.

Some reports showed that adjunctive mosapride improves the participant's compliance<sup>[7-9]</sup>. However, the effects of adjunctive mosapride on the improvement of patient's stress were not objectively analyzed. Questionnaires for patients are usually used for such assessment. However, such an assessment depends on the patient's character and sometimes yields subjective results. Salivary alpha-amylase (SAA) monitoring was developed to objectively assess psychological stress<sup>[12-16]</sup>. The identification of peripheral biomarkers reflecting autonomic activity has lagged. SAA has emerged as a surrogate marker of sympathetic nervous system activity<sup>[15]</sup>. Although SAA is not a direct product of the sympathetic nervous system, there are several studies showing the involvement of the autonomic nervous system, particularly its sympathetic branch, in the SAA secretion process<sup>[15]</sup>.

This study was conducted to evaluate the efficacy of adjunctive mosapride in PEG solution for colonoscopy preparation. The stress of patients was analyzed objectively and subjectively. Adjunctive mosapride in PEG solution for colonoscopy preparation showed efficacy in the bowel cleansing. Salivary alpha-amylase showed that PEG drinking was stressful for participants although mosapride could not show the efficacy by SAA.

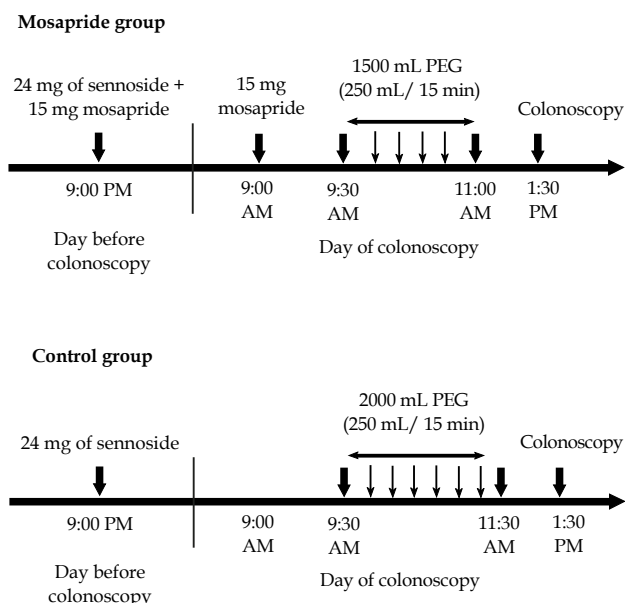
## PATIENTS AND METHODS

### Study population

Consecutive patients 20-70 years of age that were scheduled for colonoscopy at Gunma University Hospital were included to this study. The purpose of colonoscopy was to screen for such symptoms as occult blood stool, abdominal discomfort or constipation, etc. Patients with significant comorbidities of bowel obstruction or stenosis, known allergy to mosapride or PEG solution, history of gastric or colonic surgery, or pregnancy were excluded. A gastroenterologist assessed patient eligibility, and written informed consent was obtained. Patients were randomly allocated to receive one of two bowel preparation regimens indicated in the next section. This study was a randomized, prospective, open-label study, and was reviewed and approved by the ethics committee of Gunma University Hospital.

### Bowel preparation regimens

Bowel preparation regimens are shown in figure 1. Briefly, participants were divided into two groups. All of the patients received the 24 mg of sennoside (Novartis Pharma K.K. Tokyo, Japan) at 9:00 p.m. the day before colonoscopy. Furthermore, participants in the mosapride group took 15 mg of mosapride (Gasmotin; Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) orally at the same time (9:00 p.m. at the day before colonoscopy). All participants came to the endoscopic unit on the day of the colonoscopy, and received in-hospital bowel preparation. In-hospital preparation ensured the uniformity of the procedures. All patients were treated within the same time schedules and that reduced the influence of circadian changes of SAA. The mosapride group took 15 mg mosapride orally at 30 min before drinking the PEG (9:00 a.m. at the day of colonoscopy). Participants in the mosapride group started to drink 1500 mL of PEG solution (Niflec; Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) after 30 min (9:30 a.m. at the day for colonoscopy). The intended drinking speed was 250 mL every 15 min. Participants in the control group started to drink 2000 mL of the PEG solution at 9:30 a.m. The intended drinking speed was same as that in the mosapride group. Patients that excreted a solid stool with muddy excretions or no excretion at 1 h after finishing the PEG solution received an additional preparation, such as an enema.



**Figure 1** Regimens for bowel preparation used in this study.

### Evaluation of bowel preparation and time for colonoscopy

The efficacy of bowel preparation was assessed as: (1) Excellent (small volume of clear liquid, or more than 95% of colonic surface observed); (2) between Excellent and Good; (3) Good (large volume of clear liquid, but more than 90% of surface observed); (4) between Good and Fair; (5) Fair (some semisolid stool that could be suctioned or washed away, but more than 90% of surface observed); (6) Poor (some semisolid stool that could not be suctioned or washed away, and less than 90% of surface observed); and (7) Inadequate (repeat preparation and colonoscopy necessary). The bowel preparation status was scored "Excellent" as 1, "Excellent to Good" as 2, "Good" as 3, "Good to Fair" as 4, "Fair" as 5, "Poor" as 6, and "Inadequate" as 7. The bowel preparation status scores were compared and a low score indicated better preparation. The assessment of bowel preparation was also divided into two categories: optimal and non-optimal. Bowel preparations rated as excellent to fair were considered optimal; poor to inadequate ratings were considered non-optimal. The ratios of optimal and non-optimal were also evaluated.

The efficacy of bowel preparation was also assessed by sub-categories, residual stool, residual liquid, and bubbles. These 3 sub-categories were also scored as 1 to 7; "Excellent to Good" as 2, "Good" as 3, "Good to Fair" as 4, "Fair" as 5, "Poor" as 6, and "Inadequate" as 7. The endoscopist performing the procedure and one more observer determined the score after colonoscopy by mutual agreement. Examination times were established as: insertion time was the time required to reach the cecum and the length of the examination was the time required to complete the colonoscopy.

### Questionnaire for patient tolerance

Participants answered a questionnaire concerning the patients' characteristics, tolerability, and acceptability of bowel preparation. The tolerability was scored using a visual analogue scale (VAS) of discomfort; no discomfort as 1, felt slight discomfort as 3, felt discomfort as 5, felt considerable discomfort as 7, and could not drink all of the PEG solution because of severe discomfort as 9. Participants scored the scale after bowel preparation. Therefore, a small score indicated better tolerability. The occurrence of subjective symptoms while drinking PEG solution, such as nausea, vomiting, fullness, abdominal pain, palpitations or chest discomfort were also

recorded. The reasons for discomfort, such as the taste or volume of PEG solution were recorded. The amount of PEG solution consumed and the time from the first drink were recorded when patients felt discomfort. The amount of PEG solution consumed and time from the first drink were estimated as the maximum amount and times in patients that felt no discomfort. Therefore, those were estimated to be 1 500 mL and 90 min in the mosapride group, and 2 000 mL and 120 min in the control group, respectively.

### Stress markers

SAA was measured as a stress marker. Saliva was collected at 0, 30, 60, and 120 min from start of drinking the PEG solution<sup>[17]</sup>. The samples were frozen at  $-20^{\circ}\text{C}$  from the completion of the session until the analyses took place. The concentration of SAA was measured by an enzyme kinetic method according to the protocol specified by Rohleder *et al*<sup>[18]</sup>.

### Statistical analysis

The data are expressed as the mean $\pm$ SD. The data were analyzed using Fisher's exact probability test, and the Mann-Whitney's U-test. A *P* value less than 0.05 was considered to be significant.

## RESULTS

### Patient characteristics and colonoscopy

A total of 50 patients were randomized into two groups. Two patients were excluded based on either the exclusion criteria or sampling errors. The baseline characteristics of the patients in the two groups are shown in table 1. There were no significant differences in the sex, age and common use of laxatives between the mosapride and control groups. The total observation time for colonoscopy was  $39.6\pm 15.6$  min in the control group and  $39.0\pm 25.1$  min in the mosapride group. The time to reach the cecum was  $34.4\pm 19.8$  min in the control group and  $32.9\pm 25.2$  min in the mosapride group, respectively. The time needed for total observation or time to reach the cecum showed no differences between the mosapride and control groups.

The time needed to consume the PEG was  $132.5\pm 17.5$  min in the control group and  $53.1\pm 21.9$  min in the mosapride group, respectively. The time needed to consume the PEG was significantly shorter in the mosapride group because the amount of PEG solution was smaller in the mosapride group. One of 24 participants of the control group could not drink all of the PEG solution. All participants in the mosapride group could drink all of the PEG solution.

### Bowel cleansing efficacy

The efficacy of bowel preparation is shown in table 2. The mean bowel preparation status score was  $2.9\pm 1.2$  in the mosapride group and  $3.5\pm 1.2$  in the control group. The bowel preparation status score in the mosapride group was significantly better than the control group ( $P<0.05$ ). The bowel preparation status was analyzed by sub-categories including residual stool, residual liquid, bubbles and spasm. Although the mosapride group tended to have efficacy in the sub-categories, there were no significant differences between the two groups. There were no significant differences between the mosapride and control groups in the number of defecations from 9 p.m. of the day before colonoscopy to 9 a.m. of the day of colonoscopy. The number of defecations tended to be larger in the mosapride group, although it did not reach statistical significance. Therefore, the mosapride group had similar or better bowel cleansing efficacy in comparison to the control group.

**Table 1** Characteristics of the patients in the mosapride and control groups.

		Control group	Mosapride group	<i>P</i> value
Number of patients	N	24	24	
Sex	male/female	10/14	15/9	N.S.
Age	years	$49.2\pm 17.1$	$53.1\pm 12.4$	N.S.
Total observation time	min	$39.6\pm 15.6$	$39.0\pm 25.1$	N.S.
Time reached to caecum	min	$34.4\pm 19.8$	$32.9\pm 25.2$	N.S.
PEG drinking time	min	$132.5\pm 17.5$	$53.1\pm 21.9$	$P<0.05$
Common use of laxative	yes/no	6/18	4/20	N.S.

**Table 2** The efficacy of bowel preparation between the mosapride and control groups.

		Control group	Mosapride group	<i>P</i> value
Total		$3.5\pm 1.2$	$2.9\pm 1.2$	$P<0.05$
	Residual stool	$2.6\pm 1.3$	$2.1\pm 1.0$	N.S.
	Residual liquid	$3.2\pm 1.3$	$2.7\pm 1.0$	N.S.
	Bubbles	$2.4\pm 0.9$	$2.0\pm 0.8$	N.S.
	Spasm	$2.8\pm 1.1$	$2.6\pm 1.1$	N.S.
Optimal/non optimal		24/0	23/1	N.S.
The number of defecation	N	$1.0\pm 1.2$	$1.3\pm 1.2$	N.S.

### Patient tolerability and safety

The results of the questionnaire concerning the tolerability of bowel preparation showed the VAS score of discomfort to be  $3.6\pm 1.2$  in the mosapride group and  $4.9\pm 2.4$  in the control group (Table 3). The VAS scores of discomfort were significantly better in the mosapride group in comparison to the control group ( $P<0.05$ ). The amount of PEG solution consumed when participants felt discomfort was  $11\ 600\pm 360$  mL in the mosapride group and  $1270\pm 468$  mL in the control group. There were no significant differences in the amount of PEG solution consumed when the participants felt discomfort. The time when participants felt discomfort from the first drink was  $72.8\pm 26.6$  min in the mosapride group and  $82.4\pm 29.7$  min in the control group. There were no differences in the time between the mosapride group and control group.

Nineteen of the 24 participants (79.2%) felt discomfort in the mosapride group, and 23 of the 24 participants (95.8%) felt discomfort in the control group. There were no significant differences. Fifteen of the 24 participants (62.5%) in the control group felt discomfort with the volume of PEG solution. On the other hand, only 8 of 24 participants (33.3%) in mosapride group complained of the volume of PEG solution. The ratio of participants feeling discomfort associated with the PEG volume was significantly lower in the mosapride group in comparison to the control group ( $P<0.05$ ). The volume of PEG solutions was a significant discomfort factor in the control group.

The frequency of uncomfortable abdominal symptoms such as nausea, abdominal distention, and abdominal pains are shown in table 3. None of the 24 participants (0%) felt nausea in the mosapride group and 9 of the 24 patients (37.5%) felt nausea in the control group. The incidence of participants that felt nausea was significantly higher in the control group ( $P<0.05$ ).

### Stress markers

Table 4 shows the titer of SAA before and during bowel preparation as an objective stress marker. SAA increased with consumption of PEG in both the mosapride and control groups. SAA showed a significant increase at 120 min in comparison the before consumption ( $P<0.05$ ). This result indicates that the bowel preparation with PEG solution itself was stressful for the participants. There were no differences in the SAA between the mosapride group and control group. These results showed that drinking PEG was stressful for participants. However, mosapride could not reduce the stress analyzed by SAA.

**Table 3** The comparison of abdominal discomfort between the mosapride and control groups.

		Control group	Mosapride group	P value
Visual analogue scale (VAS) for discomfort	Range 1-9	4.9±2.4	3.6±1.2	<i>P</i> <0.05
The amount of PEG solution which participant feel discomfort	mL	1270±468	1160±360	N.S.
Time when participant feel discomfort from the start drinking	min	82.3 ±9.7	72.8±26.6	N.S.
The number of participant who felt discomfort	yes/no	23/1	19/5	N.S.
The reason of discomfort	Taste of PEG solution	8	11	<i>P</i> <0.05
	Amount of PEG solution	5	0	
	Both	10	8	
Uncomfortable abdominal symptoms	Nausea	9	0	<i>P</i> <0.05
	Abdominal distension	8	5	
	Abdominal pain	0	1	

## DISCUSSION

This study showed that the efficacy, safety and tolerability of mosapride as an adjunct to PEG solution for colonoscopy preparation. Adjunctive mosapride was useful for bowel preparation. An objective parameter showed that bowel preparation was stressful for participants. However, the results did not show an advantage in the mosapride group by SAA. The VAS score was more sensitive than the SAA in showing the differences between the mosapride and control groups. The reasons for the discomfort in the control group were related to the amount of PEG solution. The ratio of participants feeling discomfort associated with the volume of the PEG was significantly lower in the mosapride group in comparison to the control group. The 500 mL difference between the control and mosapride groups was significant in the participant's complaint in this study. The tolerance of the PEG solution was better at less than 1 500 mL in view from these results. Although the amounts of PEG solution were smaller in mosapride group, there were no differences in the bowel cleansing efficacy between the mosapride and control groups. Therefore, the regimen of adjunctive mosapride with PEG solution for bowel preparation used in this study was appropriate. Tajika *et al*<sup>[9]</sup> also reported the usefulness of adjunctive mosapride in the rate of optimal preparation.

The beneficial effect of mosapride on gastric emptying was expected to ameliorate nausea, vomiting, and fullness of the abdomen during bowel preparation. Mishima *et al*<sup>[8]</sup> showed that the administration of mosapride prior to PEG solution significantly decreased the incidence of uncomfortable abdominal symptoms. The frequency of patients that complained the nausea in the current series was significantly lower in the mosapride group.

In the present study, 30 mg of mosapride was administered (15 mg twice, 12 hour interval) for colonoscopy preparation. The recommended usual daily dosage of mosapride for adult patients with chronic gastritis is 15 mg in Japan. No obvious adverse effects of mosapride were observed in this study. The effects of mosapride are reported to be dose-dependent<sup>[19]</sup>. Additional studies that address the optimal dosage and timing of administration of mosapride may be required to clarify the optimal regimen for colonoscopy.

The use of a VAS or questionnaire for patients is common during stress assessments. Monitoring the salivary alpha-amylase (SAA) level was recently introduced as a convenient method to objectively assess psychological stress<sup>[12-14]</sup>. Peripheral biomarkers reflecting autonomic activity had been lacking, and the emergence of SAA has provided a surrogate marker of sympathetic nervous system activity. SAA responds to both physical and psychological stressors, which correspond to the response patterns of the sympathetic nervous system. The pharmacological and electrophysiological literature shows the pathways that lead to the secretion of SAA are clearly sympathetic/parasympathetic in nature<sup>[15-18]</sup>. The findings of the association between SAA and the sympathetic nervous system indicate that SAA can function as a useful biomarker in acute and

**Table 4** Salivary alpha-amylase before and during bowel preparation.

		Control group	Mosapride group	P value
Salivary alpha-amylase	×10 <sup>4</sup> U/mL			
	Before	22.9±12.6	20.1±12.3	N.S.
	30 min	19.5±11.7	24.1±15.0	N.S.
	60 min	25.0±14.0	24.7±20.7	N.S.
	120 min	29.9±15.6 <sup>1</sup>	32.6±25.5 <sup>1</sup>	N.S.

<sup>1</sup>: *P*<0.05 in comparison to the score before bowel preparation.

chronic stress studies<sup>[15-18]</sup>. This study showed that SAA increased with the consumption of PEG in both the mosapride and control groups. This result means bowel preparation with PEG solution itself was stressful for the participants. The stress markers significantly increased in both groups when the amount of PEG solution was over 1 500 mL. Therefore, less than 1 500 mL PEG solution was better, based on the stress marker. Therefore, the regimen selected in this study with 1 500 mL PEG solution and mosapride were tolerable based on the stress marker. However, it did not show any significant differences in SAA between the control and mosapride groups. The small sample size may have influenced these results in SAA. A larger sample size may therefore produce differences results in SAA. On the other hand, the VAS score showed significant differences between the control and mosapride groups. The sensitivity of the VAS score may be higher than SAA in this study. However, this discrepancy between objective and subjective stress markers needs further evaluation.

In conclusion, this study demonstrated that the co-administration of mosapride with PEG solution improves the quality of bowel preparation for colonoscopy. Mosapride was an effective and safe adjunct to PEG that led to improve the quality of bowel preparation and reduced the stress of the participants.

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