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Efficacy of Prokinetic Agents in Improving Bowel Preparation for Colonoscopy

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Key Words
Colonoscopy · Bowel cleansing · Mosapride citrate · Itopride hydrochloride

Abstract
Background and Aim: Colonoscopy plays an important role in the diagnosis and treatment of gastrointestinal illness in both Western countries and Japan. However, preparative bowel cleansing for colonoscopy is frequently troublesome for elderly and/or constipated patients, since they must drink larger volumes of lavage solution for adequate cleansing. We investigated the use of prokinetic agents for improving the efficacy and tolerability of bowel cleansing prior to colonoscopy. ***Methods:*** 613 patients were divided into two groups according to oral lavage solution used (polyethylene glycol or magnesium citrate), and were further randomized to receive either vehicle (100 ml water) alone, vehicle with 5 mg mosapride citrate, or vehicle with 50 mg itopride hydrochloride 30 min before administration of lavage solution. Experimental parameters included bowel cleansing quality, times to first defecation and completion of bowel cleansing, and incidence of uncomfortable abdominal symptoms during colonoscopy preparation. ***Results:*** Administration of mosapride citrate or itopride hydrochloride prior to oral lavage solution did not significantly improve bowel cleansing quality. However, statistically significantly fewer uncomfortable abdominal symptoms were found in patients who received mosapride citrate or itopride hydrochloride versus vehicle alone. ***Conclusion:*** Prokinetic agents effectively decreased the incidence of uncomfortable abdominal symptoms experienced during colonoscopy preparation.

Introduction

The incidence of colon cancer and inflammatory bowel disease is steadily increasing not only in Western countries but also in Asia. The role of colonoscopy in the diagnosis and treatment of these diseases is also expanding. However, poor tolerance and adverse effect were often found in the bowel preparation of colonoscopy for elderly patients and those with constipation, since they are often required to drink larger volumes of lavage solution prior to the bowel cleansing procedure. Both polyethylene glycol (PEG) electrolyte solution and magnesium citrate (MGC) solution have been widely used in Japan as lavage solutions for bowel cleansing [1–4]. About 2,000 ml of these solutions are usually required for adequate

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bowel preparation. As a result, we have encountered patients with insufficient bowel cleansing due to inadequate intake of lavage solution. Inadequate bowel preparation decreases the sensitivity of colonoscopy and increases the difficulty of the procedure [5]. Therefore, modification of bowel preparation methods is required to increase their efficacy and tolerability [6, 7].

One way to improve bowel preparation is to coadminister a prokinetic agent with oral lavage solution. Cisapride has been evaluated as a potential prokinetic candidate for bowel preparation [8–12]; however, it is no longer used in this setting due to its serious side effects. The value of other prokinetics, including mosapride citrate and itopride hydrochloride, has not yet been fully investigated [13, 14]. Mosapride citrate is a selective agonist for 5-hydroxytryptamine 4 (5-HT4) receptors and induces the peristalses in the upper and lower gastrointestinal tract. The 5-HT4 receptor has been proven to be located in human colon, and agonists for 5-HT4 receptor initiate peristaltic reflexes not only in rat and guinea pig but also in human intestine [15–17]. On the other hand, itopride hydrochloride is a benzamide derivative and acts through both dopamine D2 receptor antagonism and acetylcholinesterase inhibition. Previous studies have revealed that itopride hydrochloride stimulates the colonic peristalsis with propelling colonic luminal contents [18, 19].

In the present study, we have investigated the efficacy and tolerability of coadministering these two prokinetic agents with oral lavage solution for bowel preparation for colonoscopy.

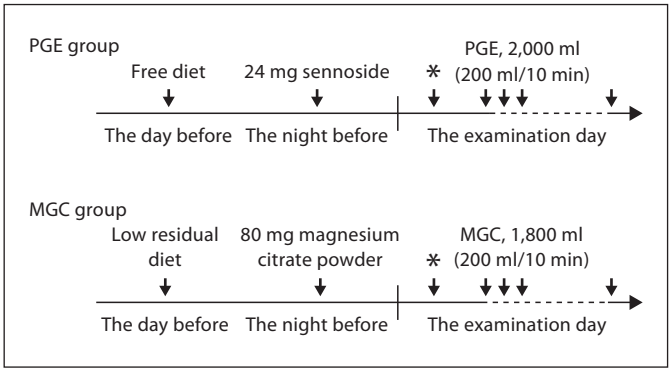


Fig. 1. The time schedule for bowel preparation for colonoscopy. The asterisk signifies dose of 100 ml water alone, water with 5 mg mosapride citrate, or 50 mg itopride hydrochloride 30 min before administration of lavage solution. PGE = Polyethylene glycol electrolyte solution; MGC = magnesium citrate solution.

Patients and Methods

Study Protocol

From November 2005 to March 2007, 613 patients who agreed to participate in this study were enrolled. Patients were initially divided into two groups according to which lavage solution – PEG or MGC – was administered. The protocol of bowel preparation for colonoscopy in our institution had decided that patients who underwent colonoscopy for the first time and/or who suffered from severe constipation were assigned to the MGC group, while the remaining patients were assigned to the PEG group. Within each of these groups, patients were randomly assigned to three subgroups by the envelope method: administration of vehicle (100 ml water) alone (PEG-v, MGC-v), vehicle with 5 mg mosapride citrate (PEG-m, MGC-m), or vehicle with 50 mg itopride hydrochloride (PEG-i, MGC-i); these agents were given with 100 ml of water 30 min before the administration of oral lavage solution. The patients were not blinded to the grouping. Prokinetics were explained as laxatives to the patients.

Patients in the PEG group received 24 mg sennoside the night before the examination, and drank 200 ml PEG solution (Niflec®, Ajinomoto Pharma Co., Ltd., Tokyo, Japan) every 10 min on the examination day, for a total intake of 2,000 ml PEG solution. Those in the MGC group followed a low residual diet (Enimaclin®, Glico Co., Tokyo, Japan) for bowel cleansing the day before the examination and took 80 g MGC powder the night before, instead of 24 mg sennoside in the PEG group. These patients then drank 200 ml MGC solution (Magcorol-P®, Horii Pharmaceutical Ind., Ltd., Osaka, Japan) every 10 min on the examination day, for a total intake of 1,800 ml MGC solution. The time schedule of bowel preparation for colonoscopy in both the PEG and MGC groups is shown figure 1. Patients who agreed to participate in this study were explained the protocol and time schedule of bowel preparation 1 or 2 weeks before the colonoscopic examination. Patients were not informed about the group randomization or the kind of drugs until the day of colonoscopy.

Assessment of Prokinetic Effects

Prokinetic factors evaluated included bowel cleansing quality, time to first defecation, time to completion of bowel cleansing, and occurrence of unpleasant abdominal symptoms during the colonic preparation. They were compared among the vehicle alone, mosapride citrate and itopride hydrochloride in both the PEG and MGC groups, respectively. Nine expert endoscopists were enrolled in this study, and they judged the level of bowel cleansing without prior knowledge of the preparation method. The quality of bowel cleansing was categorized into five levels as summarized in table 1: level 1 (very poor), impossible to examine due to solid or muddy stool throughout the colon; level 2 (poor), solid or muddy stool in at least half of the colon; level 3 (fair), turbid cleansing solution throughout the entire colon; level 4 (good), turbid cleansing solution in at least half of the colon, and level 5 (excellent), little to no transparent cleansing solution. The cleansing level of bowel preparation was decided by agreement with at least 2 out of 3 endoscopists who were randomly selected from 9 enrolled endoscopists. Patients were also requested to answer questionnaires about unpleasant abdominal symptoms including nausea, vomiting, bloating, and abdominal pain experienced during bowel preparation. Patients checked the degree of abdominal

Table 1. Bowel cleansing quality as assessed with endoscopy

Level 1	very poor	impossible to examine due to solid or muddy stool throughout the colon
Level 2	poor	solid or muddy stool in at least half of the colon
Level 3	fair	turbid cleansing solution throughout the colon
Level 4	good	turbid cleansing solution in at least half of the colon
Level 5	excellent	little to no transparent cleansing solution

symptom as 'none', 'moderate' and 'severe' in each of the four categories. If the 'moderate' and 'severe' were checked, the abdominal symptom was judged as an unpleasant one. They were classified as patients with unpleasant symptoms when at least one symptom out of the four categories was 'moderate' or 'severe'.

Effect of Prokinetics on Gastric Emptying

Gastric emptying was assessed in 7 healthy subjects after administration of vehicle alone, 5 mg mosapride citrate, or 50 mg itopride hydrochloride. A 2-week interval between testing was instituted to allow for drug clearance. Gastric emptying was measured using a [^{13}C]-acetate breath test. After overnight fasting, each subject took each drug orally with 100 ml water 30 min before ingestion of the test meal. The caloric liquid meal (RACOL® 200 ml, 200 kcal, Otsuka Pharmaceuticals Co., Ltd., Tokyo, Japan) with 100 mg of [^{13}C] acetate was used as a test meal. Breath samples were taken before and after ingestion of the test meal: at baseline, at 5-min intervals during the first 20 min, at 10-min intervals during the next 40 min, and at 15-min intervals for the final 60 min; thus, samples were collected at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, and 120 min. The concentration of $^{13}CO_2$ in collected breath samples was measured by isotope-selective nondispersive infrared spectrometry (UBiT IR 300, Otsuka Electronics Co., Ltd., Osaka). T_{max}-calc value was calculated as an index of gastric emptying speed using analysis software (Microsoft® Office Excel 2003, Microsoft Japan Co., Tokyo) from a $^{13}CO_2$ breath excretion curve as described in our previous report [20, 21]. Smaller T_{max}-calc values indicate faster gastric emptying.

The study protocol was approved by the ethics committee of the Shimane University School of Medicine. Written informed consent was obtained from all participants.

Statistical Analysis

The χ^2 test and unpaired t test (either Student's t test or Welch's test) were used to test for significant differences in all categorical data. When unequal variances were found in the analyzed data, a significant difference was statistically calculated by Welch's test rather than Student's t test. Statistical comparisons of data within each group were performed using the Wilcoxon signed rank test when the Friedman test showed significant differences. A p value <0.05 was considered to be significant. All statistical analyses were performed using Statistical Analysis Software (SPSS, version 12.0 for the PC, SPSS Japan, Inc.).

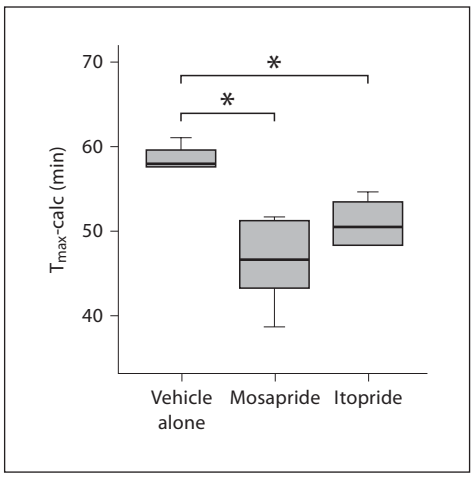


Fig. 2. T_{max}-calc values calculated using the [^{13}C]-acetate breath test in 7 healthy subjects who received vehicle alone, mosapride citrate, or itopride hydrochloride. Mosapride citrate and itopride hydrochloride were shown to significantly shorten the time of T_{max}-calc (* $p < 0.05$; $n = 7$). Each box encompasses data from the 25th to 75th percentiles; the bold line within the box equals the median value. Lines above and below each box represent the 90th and 10th percentile values, respectively.

Results

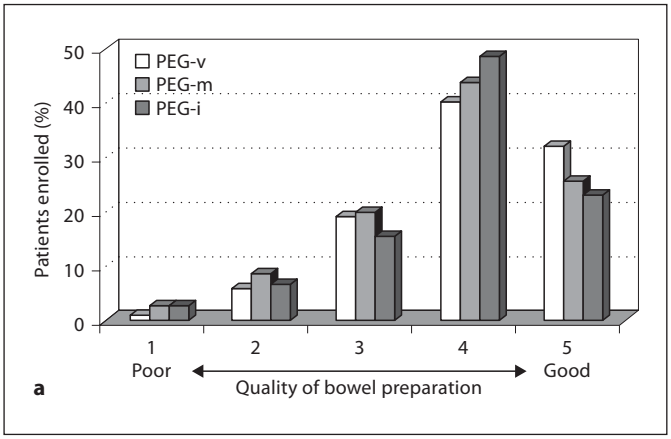
Effect of Prokinetics on Gastric Emptying

The effects of mosapride citrate and itopride hydrochloride on gastric emptying in 7 healthy subjects, as investigated by the crossover analysis, are shown in figure 2. The T_{max} values obtained after vehicle, mosapride citrate, and itopride hydrochloride administration were 57.8 ± 3.1, 46.3 ± 4.7, and 49.4 ± 5.6 min, respectively. Mosapride citrate and itopride hydrochloride were both shown to significantly shorten T_{max}-calc compared to vehicle ($p < 0.05$).

Effect of Prokinetics on Bowel Preparation

A total of 613 patients were assigned to six treatment subgroups, as shown in table 2. The prevalence of constipation, history of abdominal surgery, and obesity did not differ within the three PEG-administered subgroups or within the three MGC-administered subgroups.

The quality of bowel preparation for each group is shown in figure 3. In both the PEG and MGC groups, administration of mosapride citrate or itopride hydrochloride prior to oral lavage solution tended to improve bowel cleansing quality, although no statistically significant difference was observed with respect to the cleansing level.



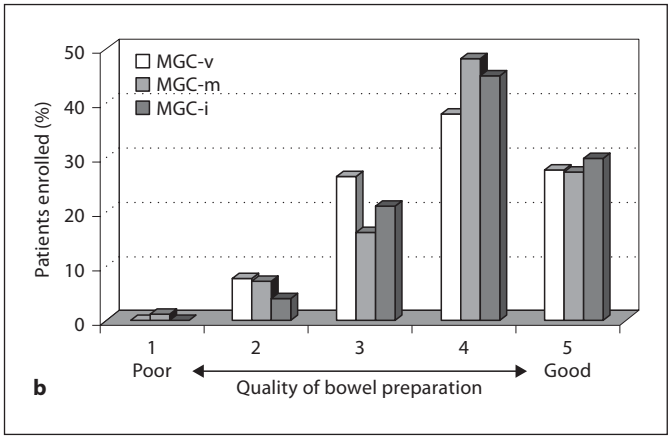


Fig. 3. a Quality of bowel preparation in patients in the PEG group. Administration of mosapride citrate or itopride hydrochloride prior to oral lavage solution tended to improve bowel cleansing quality, although the improvements were not statistically significant. PEG-v = Treatment with 2,000 ml PEG alone; PEG-m = treatment with 5 mg mosapride citrate followed by 2,000 ml PEG; PEG-i = treatment with 50 mg itopride hydrochloride followed by 2,000 ml PEG. **b** Quality of bowel preparation in patients in the MGC group. Administration of mosapride citrate or itopride hydrochloride prior to oral lavage solution tended to improve bowel cleansing quality, although the improvements were not statistically significant. MGC-v = Treatment with 1,800 ml MGC alone; MGC-m = treatment with 5 mg mosapride citrate followed by 1,800 ml MGC; MGC-i = treatment with 50 mg itopride hydrochloride followed by 1,800 ml MGC.

Table 2. Patient characteristics

Characteristic	PEG-v	PEG-m	PEG-i	MGC-v	MGC-m	MGC-i	p value
Number	99	103	103	105	99	104	NS
Males, %	62.6	60.9	65.7	51.4	50.5	58.7	NS
Mean age ± SD, years	64.1 ± 11.6	62.4 ± 12.8	66.1 ± 12.1	61.8 ± 14.4	64.6 ± 12.9	65.1 ± 12.2	NS

For abbreviations, see figure 3.

As shown in figure 4, the average time to first defecation from the start of oral lavage was 64.2 ± 37.6, 61.5 ± 35.8, 62.5 ± 36.9, 62 ± 42.6, 51.9 ± 36.4, and 55.3 ± 30 min in the PEG-v, PEG-m, PEG-i, MGC-v, MGC-m, and MGC-i groups, respectively. In the MCG groups, coadministration of mosapride citrate or itopride hydrochloride tended to shorten defecation time, but no statistically significant difference was found.

As shown in figure 5, the average time for completion of bowel preparation was 180.2 ± 68.4, 178.6 ± 64.6, 185.5 ± 60, 171.3 ± 67.8, 167.8 ± 60.9, and 168.6 ± 58.5 min in the PEG-v, PEG-m, PEG-i, MGC-v, MGC-m, and MGC-i groups, respectively. In the MCG groups, coadministration of mosapride citrate and itopride hydrochloride also tended to shorten bowel preparation time. The average number of defecations and the total volume required for completion of bowel preparation did not differ within the three PEG subgroups or within the three MGC subgroups.

Constipation, history of abdominal surgery, and body mass index did not affect the quality of bowel preparation or the required time for bowel preparation. A total of 9, 4, 2, 8, 2, and 3 patients suffered from unpleasant abdominal symptoms during preparation in the PEG-v, PEG-m, PEG-i, MGC-v, MGC-m, and MGC-i groups, respectively. In the PEG group, the incidence of their symptoms was 23.2, 16.6 and 10.2% in the vehicle alone, mosapride citrate and itopride hydrochloride groups, respectively. In MGC group, the incidence of their symptoms was 22.9, 14.3 and 12.5% in the vehicle alone, mosapride citrate and itopride hydrochloride groups, respectively. A significantly decreased incidence of unpleasant abdominal

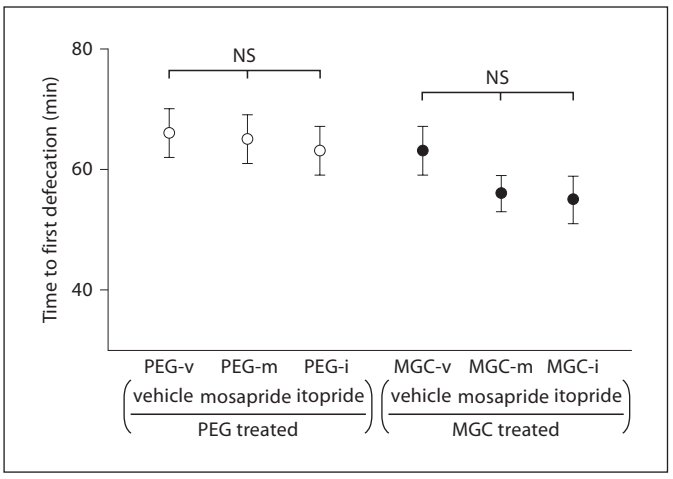


Fig. 4. Time to first defecation. The shortest times occurred in patients who received MCG with mosapride citrate or itopride hydrochloride, although statistical significance was not reached. Circles represent mean values; bars indicate standard error ranges. NS = Not significant.

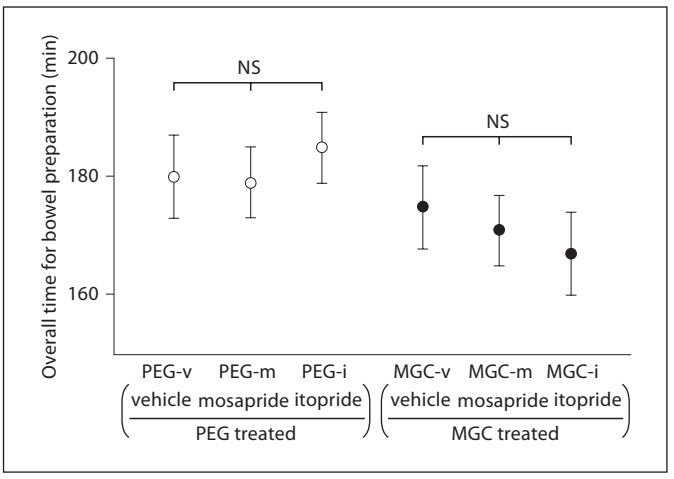


Fig. 5. Overall time required for completion of bowel preparation. Shorter bowel preparation times occurred in patients who received MCG with mosapride citrate or itopride hydrochloride, although statistical significance was not reached. Circles represent mean values; bars indicate standard error ranges. NS = Not significant.

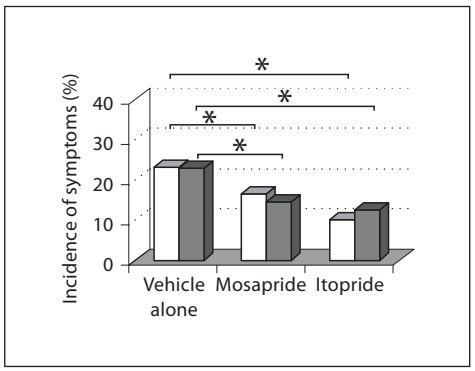


Fig. 6. Incidence of unpleasant abdominal symptoms during bowel preparation. Patients who received either mosapride citrate or itopride hydrochloride coadministered with lavage solution experienced fewer symptoms than patients who received vehicle alone in both the PEG (□) and MGC (▨) groups (* $p < 0.05$).

symptoms occurred in the mosapride citrate and itopride hydrochloride groups compared to the vehicle groups in both the PEG and MGC groups ($p < 0.05$), as shown in figure 6. Moreover, no adverse effect that was specific to the administration of 5 mg mosapride citrate or 50 mg itopride hydrochloride was found in any of the enrolled patients.

Discussion

Complete bowel preparation prior to colonoscopy is essential for an accurate diagnosis and treatment of colonic lesions. The introduction of PEG and MGC as oral lavage solutions has improved the quality and feasibility of precolonoscopic bowel preparation. However, the requirement for oral lavage solution volume, as high as 2,000 ml, often causes unpleasant abdominal symptoms and preparation failure due to intolerance to the lavage solution [4–6].

Coadministration of cisapride or laxatives such as sennnoside and bisacodyl with oral lavage solution has been reported to be useful for effective bowel preparation [8–12]. Cisapride stimulates acetylcholine release from the postganglionic myenteric plexus as well as gastrointestinal peristaltic activity. Cisapride has been used as a prokinetic agent along with lavage solution for bowel preparation and has been demonstrated to shorten the required time period for precolonoscopic bowel preparation and to decrease the lavage solution volume [8, 9], although these results have been difficult to reproduce [11, 22]. However, use of cisapride in this setting is associated with serious unexpected side effects, so it has been withdrawn from the market [23, 24]. Other prokinetic agents, including domperidone and tegaserod, have been coadministered with oral lavage solution in an attempt to im-

prove the quality of bowel preparation and patient tolerance to lavage solution [25]. However, the required volume of these agents has not yet been clearly established, and the results of studies that have evaluated these agents have thus far been contradictory [13, 14].

In the present study, mosapride citrate was selected from several prokinetic agents because it is a highly selective agonist for 5-HT4 receptors and does not influence other receptors, including dopamine D2 receptors. This specificity is expected to decrease uncomfortable side effects related to other classes of receptors, such as those that are observed with drug-induced parkinsonism [26]. A previous analysis has revealed that the combination of mosapride citrate with PEG electrolyte solution and sennoside successfully improves bowel preparation [27]. In addition to its clear stimulatory effect on the peristaltic action of the upper gastrointestinal tract, mosapride citrate has been reported to stimulate colonic motility through 5-HT4 receptors [15–17]. Itopride hydrochloride has been also reported to stimulate colonic motor activity and to shorten colonic transit time through inhibition of dopamine D2 receptors and acetylcholine esterase [18, 19].

As a fundamental study, we firstly evaluated by the analysis of the gastric emptying test whether the dosage and the dose timing of mosapride citrate and itopride hydrochloride were adequate or not. Resultantly, it was fully proven that both 5 mg mosapride citrate and 50 mg itopride hydrochloride showed a statistically significant effectiveness for the gastric emptying 30 min after their administration. While coadministration of mosapride citrate and itopride hydrochloride with lavage solution accelerated gastric emptying, these agents did not markedly improve the quality of bowel preparation. Further, although both prokinetics shortened the required bowel preparation period in the MGC group, this did not occur to a significant degree. The drug doses and timing of coadministration used in the present study may not have been optimized to detect effects on bowel preparation. Therefore, additional studies that address optimal doses and timing of administration are required in order to clarify whether prokinetics have the potential to improve the quality of bowel preparation.

In contrast, coadministration of these prokinetics with lavage solution clearly decreased the occurrence of unpleasant symptoms caused by administration of lavage solution without increasing drug-related side effects. Therefore, mosapride citrate and itopride hydrochloride both appear to be good candidates for decreasing unfavorable adverse events and increasing tolerability during colonoscopy preparation procedures.

In summary, we have demonstrated that coadministration of mosapride citrate or itopride hydrochloride with oral lavage solution decreases unpleasant abdominal symptoms caused by the lavage solution, although it did not dramatically improve the quality of bowel preparation for colonoscopic analysis.

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