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Utility of Mosapride Citrate in Pediatric Functional Constipation with Low Bowel Movement Frequency

ABSTRACT

Mosapride citrate (Mc) is a useful prokinetic agent for pediatric functional dyspepsia in Japan. However, improvement in bowel movements has also been observed after treatment with Mc in functional constipation (FC) children. Here, we describe the first clinical research on the use of Mc for FC in a pediatric population. This retrospective study at the Division of Pediatrics in Tohoku Medical and Pharmaceutical University for two years from 2016 included eighteen pediatric FC patients with agreement of the administration of Mc (Mc group: 9 males; median age, 58 months), in whom previous treatment with conventional laxatives were ineffective. Mc (0.3 mg/kg/day) was administered in addition to Mc group. A control group, seventeen FC patients, received conventional laxatives only. Bowel movement frequency (BMF) in Mc group was significantly lower than the control group before our treatments; median 0.5 and 2 day/week, respectively. All patients in both groups achieved complete remission (CR), defined as requiring no further pharmacotherapy. According to the treatment by Mc, only treatment duration until CR showed a significant difference between Mc and the control group; median 3 and 2 months, respectively. The addition of Mc to intractable FC children is reasonable as an aim of increasing BMF.

Keywords: Bowel Movement Frequency; Child; Functional Constipation; Mosapride Citrate.

INTRODUCTION

Functional constipation (FC) in children often requires medical treatment, including pharmacotherapy. Conventional laxatives such as magnesium oxide, sodium picosulfate, lactulose, and carmellose sodium have been used for many years. However, these drugs are often ineffective for patients with intractable FC, requiring continual transanal treatments such as glycerin enemas or bisacodyl suppositories.

Mosapride citrate (Mc), a 5-HT4-receptor agonist, is a prokinetic agent that is useful for functional dyspepsia [1]. Symptoms of FD are epigastric discomfort, bloating, appetite loss, pain, or nausea. We administered Mc to pediatric FC patients with the symptoms of functional dyspepsia. This empiric treatment of some patients resulted in significant improvement in bowel movements.

In this retrospective study, we assess the effectiveness of Mc combined with the conventional laxatives for FC in a pediatric population. To our knowledge, this

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is the first clinical research on the use of Mc to treat FC in children.

MATERIALS AND METHODS

Subjects

This was a single-center retrospective cross-sectional study carried out at the Division of Pediatrics in Tohoku Medical and Pharmaceutical University. Thirty-six patients, who conformed to Rome criteria for FC and visited our center for two years from June 2016, were recruited in the study [2]. An exclusion criterion was secondary constipation due to congenital, anatomical, endocrinal, or metabolic disorders. Thirty-five patients were finally registered in the study except for one patient with lumbar lipoma and spina bifida. The included patients were divided into two groups by an informed consent according to the administration of Mc. We recommended the administration of Mc to the patients with the symptoms of FD positively. In Mc group, comprising eighteen patients with agreement of the administration, Mc (0.3 mg/kg/day in two divided doses) was added after the conventional laxatives were ineffective [3]. In a control group, comprising seventeen patients without the agreement, the conventional laxatives were used only. The conventional laxatives were administered according to weight (kg), according to a previously published guideline [4] and medical user's manuals. We obtained informed consent for all patients from patients and their caregivers. The Committee on Ethical Affairs in our center judged that the study did not have any ethical problems, because all procedures had been performed under the Health Care Services provided by Health Insurance in Japan (registry number: 2018-2-060).

The treatment was estimated as effective when the patient did not meet Rome IV FC criteria [4,5] for more than four weeks {e.g., bowel movement frequency was more than 3 days per week (BMF) or stool consistency was consistently higher than type 3 on the Bristol stool form scale (BSFS)}. De-escalation of the laxatives including Mc was performed in a step-wise manner and was started when the treatment was effective. Complete remission (CR) was defined as a laxative-free status for more than 4 weeks based on our previous clinical study and a previous article [5,6].

Methods

All data were extracted from the health records retrospectively. Survey items were sex, height (cm), weight (kg), age in months at first visit, experiencing ineffective conventional laxative treatments prior to visiting our center (EICLT), BMF and median BSFS in the last month, treatment duration until CR at our center, requiring the continual transanal treatments, and percentage achieving CR.

Analysis of the collected data was performed using "EZR" free-software program [7]. The Mann-Whitney U test was used to compare data: age in months at the first visit, height, weight, BMF, BSFS, dosage of laxatives including Mc, and treatment duration. A 2 × 2 Chi-square-test was used to analyze categorical data including sex, EICLT, and CR. *P* values <0.05 were considered significant.

RESULTS

The patient backgrounds prior to visiting our center are shown in **(Table 1)**.

Table 1: Patient characteristics prior to visiting our center.

	Mc Group (n=18)	Control Group (n=17)	*p* Value
Symptoms of Functional Dyspepsia	Positive	Negative	
Sex (Male:Female)	9:9	6:11	0.380
Age at First Visit (months)‡	58, 16-119	41, 9-101	0.083
Height (cm)‡	107.1, 76.6-140.7	93.0, 72.0-131.0	0.081
Weight (kg)‡	18.6, 9.6-30.4	14.3, 8.6-31.0	0.129
EICLT, n (%)	18 (100%)	7 (41.2%)	<0.01*
Previous Ineffective Laxatives	Mg, Pi, La, Ca	Mg, Pi, La	
Requiring the Continual Transanal Treatments, n (%)	9 (50 %)	3(17.6 %)	0.044*
BMF (days/week)‡	0.5, 0-2	2, 0-7	<0.01*
BSFS‡	1, 1-4	1, 1-4	0.268

Abbreviations; Mc: mosapride citrate, Mg: magnesium oxide, Pi: sodium picosulfate, La: lactulose, Ca: carmellose sodium, EICLT: experiencing ineffective conventional laxatives treatments, BMF: bowel movement frequency, BSFS: Bristol stool form scale. Symptoms of functional dyspepsia are epigastric discomfort, bloating, appetite loss, pain, or nausea. ‡Values presented as median, minimum-maximum unless otherwise indicated. *significant difference by *p* value

The patients were classified into two groups clearly, whether they had the symptoms of FD. All patients in Mc group had been diagnosed as intractable FC by other medical institutions because of EICLT and long disease duration until our center, median 2 years. On the other hand, none in the control group had been recognized as intractable FC because of the short disease duration, median 0.2 year. A significant difference

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between Mc and the control group was found in the percentage of EICLT (100% vs. 41.2%, respectively), requiring the continual transanal treatments (50.0 vs. 17.6%, respectively), and BMF (0.5 vs. 2 days/week, respectively). No significant difference was seen in BSFS.

The results of treatments at our center are shown in **(Table 2)**. Significant difference between two groups was recognized in the treatment duration; 3 vs. 2 months, respectively. Two patients in Mc group had poor Mc efficacy making them dependent on the continual transanal treatments. These poor responders eventually required long periods to achieve the statement without requiring the continual transanal treatments; 6 and 9 months, respectively. The poor responders were also the cause of the statistical difference seen in the treatment duration. All patients in two groups eventually achieved CR, and the longest treatment duration was 22 months in Mc group. No adverse events, including hepatic damage, occurred in any patients.

Table 2: Patient characteristics after the Treatments at Our Center.

		Mc Group (n=18)	Control Group (n=17)	*p* Value
Number and (Dosage [kg/day]) of Treatments	Mc (mg)†	18 (0.295, 0.247-0.331)	0 (0, 0-0)	ND
	Mg (g)†	10 (0.056, 0.010-0.086)	9 (0.061, 0.018-0.090)	0.483
	Pi (mg)†	7 (0.242, 0.099-0.631)	2 (0.275, 0.174-0.376)	0.497
	La (g)†	10 (0.839, 0.433-2.031)	9 (0.056, 0.010-0.086)	0.177
	Ca (g)†	1 (0.017, 0.017-0.017)	0 (0, 0-0)	ND
CR, n (%)		18 (100%)	17 (100%)	ND
Treatment Duration until CR (months)‡		3, 1-22	2, 1-5	0.023*
BMF (days/week)‡		7, 3-7	7, 3-7	0.090
BSFS‡		4, 1-6	4, 4-5	0.316

Abbreviations; Mc: mosapride citrate, Mg: magnesium oxide, Pi: sodium picosulfate, La: lactulose, Ca: carmellose sodium, CR: complete remission, BMF: bowel movement frequency, BSFS: Bristol stool form scale, ND: not determined. †Values presented as: number (median, minimum-maximum). ‡Values presented as median, minimum-maximum unless otherwise indicated. *significant difference by *p* value

DISCUSSION

Mosapride citrate has excellent efficacy in a few months for treating pediatric FC. Few studies, including those with an adult study population, have shown that Mc is effective for treating FC [8]. Okada et al. suggested Mc should be administered to pediatric patients with intractable FC; however, no literature was cited to support this point [9]. Mc is also described in the Japanese guideline for FC in children, but it has no citations supporting the recommendation [4].

BSFS, not BMF, provides a severity in mild FC [10]. Long disease duration by hard stool (low grade BSFS: 1 or 2) induces a disturbance in the colon wall, and an impaired neuronal response for bowel movement should be to decrease BMF due to delay of colonic transit time [11]. This vicious cycle leads to intractable FC, in which BMF provides the severity of FC as effectively as BSFS [4,11]. It was suggested that Mc group should show more intractable FC than the control group according to BMF. In animal studies, it was shown that the prokinetic activity of Mc is effective for constipation [12,13]. Mc was also shown to repair injured enteric neurons in a mouse [14]. In humans, it was shown that Mc enhanced rectosigmoid sensorimotor function in patients with constipation-type irritable bowel syndrome [15]. Therefore, in pediatric FC patients, Mc might also induce spontaneous bowel movements and increase BMF.

We attempted to prove the efficacy. All patients with more intractable FC than the control group, Mc group, eventually achieved CR by the improvement of BMF in **(Table 2).** If only conventional laxatives had been administered to Mc group, the percentage achieving CR would have been "zero" because of EICLT. Therefore, it is reasonable to administer Mc to intractable FC patients as an aim of increasing BMF.

This study has three limitations. First is the small number of patients. Further accumulation of cases is necessary for more detailed analysis. The second limitation is the existence of poor responders to Mc. We have no established protocol for poor responders. Currently, the continual transanal treatments are indispensable for poor responders. Because all patients in Mc group eventually achieved CR, the continuation of Mc until achieving CR should be permitted at least. Step-down therapy from the continual transanal treatments should be permitted after the improvement of BMF is achieved using a standard protocol [5]. More investigation of Mc or other prokinetic agents may remove the need for continuing the transanal treatments in poor responders. The third limitation is that the conventional laxatives in this study don't include polyethylene glycol (PEG), the first choice of pediatric FC in the world. PEG had not been approved as laxative under the Health Care Services provided by Health Insurance in Japan during the study. That is why we couldn't use PEG in this study. Because PEG has the same

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pharmacodynamics as osmotic laxatives such as magnesium oxide, PEG may reveal only restrictive efficacy in intractable FC patients with low BMF. A combination therapy of Mc and PEG is an examination subject in future.

CONCLUSION

In conclusion, we recommend that Mc administration should be added to the conventional laxatives as an option for treating intractable FC in children with low BMF.

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