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【 CASE REPORT 】

Effects of Rhubarb on Intestinal Dysmotility in Critically Ill Patients

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Abstract:
Intestinal dysmotility is a major problem in critically ill patients. This report describes the successful treatment of intestinal dysmotility with rhubarb as a laxative in six critically ill patients on mechanical ventilation. Bowel movement and defecation occurred in all patients an average of 1.8 days after the administration of powdered rhubarb. In 4 patients who also had gastric reflux, the reflux volume via nasal tube was decreased an average of 3.5 days after the initiation of rhubarb treatment, and enteral nutrition was able to be started. Rhubarb may be useful for the treatment of incompetent gastric and intestinal motility in critically ill patients.

Key words: critically ill, constipation, defecation, ICU, motility

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Introduction

Intestinal complications such as diarrhea and intestinal dysmotility as indicated by symptoms such as gastric fluid reflux, constipation, and vomiting occur in 60% or more of patients in the intensive-care unit (ICU). Constipation is also reported to occur in 2% to 25% of healthy people, but the incidence sometimes rises to 80% in critically ill patients (1). Although enteral nutrition is recommended in the early stage for critically ill patients (2), it is not possible to conduct enteral nutrition in patients with intestinal dysmotility. Furthermore, intestinal dysmotility can result in intestinal "undrained abscess" due to the abnormal proliferation of pathogenic bacteria, which can easily cause bacterial translocation leading to septic conditions and multiple organ dysfunction syndrome (3). It has been reported that constipation in ICU patients is related to prolongation of hospitalization and an increase in mortality (4, 5).

Rhubarb has been widely used as a traditional Chinese herbal medicine since ancient times. Sennoside A and other dianthrone derivatives are reported to be the active ingredients causing rhubarb's laxative effect (6). They are metabolized by β-glucosidase of enterobacterial origin and are converted into rhein anthrone, which produces the purgative activity. This is also known to have an antibacterial effect (7) and effects on nitrogen urea metabolism (8) and renal protection (9, 10). Rhubarb, which can be used as a prescribed drug "Powdered Rhubarb" (11) (Daio powder; Suzu Pharmaceutical, Osaka, Japan) in Japan, can be administered for constipation.

However, there have been few reports on the effects of rhubarb therapy in critically ill patients. Therefore, we examined the effects of rhubarb in the treatment of intestinal dysmotility in critically ill patients.

Case Reports

Case 1

A 69-year-old man was transferred from another hospital because of sepsis. When he arrived, his heart rate was 95/min, and his blood pressure was 154/81 mmHg with catecholamine therapy. His respiratory rate was 22/min, but an arterial blood gas analysis yielded a pH of 7.49, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 47.6 mmHg, and partial pressure of arterial oxygen (PaO_2) of 60.3 mmHg under oxygen support. He was intubated, and

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Table. Characteristics of the 6 Patients Treated with Rhubarb (*Daio*).

Case	1	2	3	4	5	6
Age	69	74	57	63	67	61
Sex (M/F)	M	M	M	M	F	M
Disease	Sepsis	Mediastinal gas gangrene	ARDS, Trauma	ARDS, Trauma	ARDS, Trauma	Peritonitis
APACHE II on admission	17	10	13	14	16	22
Days of constipation before treatment	4	4	4	11	3	9
Gastric residuals (ml/day) before treatment	210	-	200	-	800	290
Days of defecation after treatment	1	1	4	2	2	1
Start day of enteral nutrition after treatment	4	Continued	4	Continued	Continued	17

APACHE: Acute Physiology and Chronic Health Evaluation, ARDS: acute respiratory distress syndrome

intensive care was required.

A blood culture revealed *Stenotrophomonas maltophilia*, and laboratory tests revealed a white blood cell count of 20,700/mm^3, red blood cell count of 237×10^4/mm^3, hemoglobin of 7.3 g/dL, hematocrit of 24.3%, and platelet count of 6.3×10^4/mm^3. Sepsis was diagnosed, and carbapenem antibiotics were started. On day 3, a laxative (sodium picosulfate hydrate) was administered because he had had no stools for 3 days. There was still no defection on day 4, so rhubarb was started. On the morning of the following day, he had several stools. He subsequently continued defecation without the use of laxatives and recovered.

Case 2

A 74-year-old man was admitted with necrotizing fasciitis in the neck and mediastinum. His vital signs were heart rate 92/min, respiratory rate 23/min, blood pressure 156/62 mmHg, and blood temperature 36.2℃. Although his vital signs were relatively stable, his pH was 7.25 and blood lactate was 19 mg/dL. His white blood cell count was 13,720/mm^3 with no anemia, and his C-reactive protein level was 24 mg/dL. He had severe systemic inflammation, and his metabolic acidosis progressed. He was intubated for a procedure, and catheter drainage was performed from the neck to the mediastinum. Blood culture revealed methicillin-resistant *Staphylococcus epidermidis* and *Enterococcus* from the catheter, so vancomycin and meropenem were administered. Enteral nutrition was started on day 2, but there had been no stools. On day 4, powdered rhubarb 0.5 g 3 times/day was started. The next day, he defecated 4 times. He continued to tolerate the rhubarb safely for 34 days with continued defecation.

We also retrospectively reviewed the mechanically ventilated critically ill patients listed in Table, which included 6 patients (5 men, 1 woman; mean age, 65.2±6.1 years). Three patients had acute respiratory distress syndrome, and the other three had infectious diseases. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission was 15.3±4.1 (12). No adverse events occurred in any patient. The average number of days of constipation before using rhubarb was 5.8 (range: 3-11 days). Bowel movement and defecation occurred in all patients within an average of 1.8 (range: 1-4) days after administration of the powdered rhubarb. In 4 patients who also had gastric reflux, the average reflux was 375 (range: 200-800) mL/day. The reflux volume via nasal tube decreased an average of 3.5 (range: 1-5) days after the initiation of the rhubarb treatment, and enteral nutrition was able to be continued in three patients and started in another three patients.

Discussion

This is the first study to evaluate the effects of rhubarb in the treatment of intestinal dysmotility in critically ill patients with mechanical ventilation. All of the patients in our study defecated within 1.8 days after beginning the use of rhubarb, and 5 of the 6 patients defecated within 2 days of its administration. There were no side effects. These results suggest that rhubarb may be a promising agent for improving constipation.

In intensive care, from the viewpoint of infection prevention and improvement of immunity, enteral nutrition is recommended from an early stage, even in patients undergoing mechanical ventilation (13). It is therefore important to control intestinal motility in critically ill patients. In severe cases, decreased intestinal blood flow due to shock, hypoxemia, and other additional stresses decreases intestinal motility and induces constipation (14). Short-chain fatty acids (SCFAs) are the metabolic end products of microbiota, and they have effects on gastrointestinal motility. Disruption of the fecal microbiota and SCFAs occurs within six hours after admission (15), and these changes remain low for six weeks (16). These miscellaneous factors may contribute to the extent of refractory constipation. For treatment of constipation in intensive care, van der Spoel et al. reported that polyethylene glycol and lactulose were effective for improv-

ing constipation in 208 ICU patients with multiple organ failure (17). Further studies are needed to compare the effects of rhubarb with these agents.

The laxative mechanism of rhubarb is based on the enhancement of the motility and secretion of water and electrolytes. Frexinos et al. measured the myoelectrical activity of the descending and sigmoid colon in humans and showed that sennoside stimulates peristaltic activity (18). Beubler and Kollar reported that intraluminal prostaglandin E2 is increased by the administration of sennoside, resulting in water and electrolyte secretion (19). These effects were inhibited by indomethacin. Another involved mechanism is an antibacterial effect. Rhubarb has been reported to exert antibacterial activity against *Bacteroides fragilis* (7) and to inhibit cholera toxin activities, including adenosine diphosphate (ADP)-ribosylation and the accumulation of intraluminal fluid (20).

To induce its laxative effect, rhubarb needs to be metabolized to rhein anthrone by β-glucosidase, which is produced by gut microbiota. Nijs et al. reported that germ-free rats have a larger cecal weight and longer intestinal transit time and receive no laxative effect from rhein anthrone than the rats which have gut microbiota (21). The difference in laxative effects based on the gut microbiota is expected. Indeed, when intestinal flora in patients with systemic inflammatory response syndrome are quantitatively assessed, the total numbers of obligate anaerobes are significantly lower than those of normal controls, and this is associated with mortality (22, 23). In terms of the mechanism of absorption, Kon et al. reported that rhein anthrone activates macrophages, which can reduce the aquaporin-3 expression, inhibit the absorption of water, and lead to a laxative effect (24). Thus, periods of constipation may depend on both the severity of disease and the SCFAs generated by the altered microbiota. In addition, periods of defecation may depend on the β-glucosidase generated by the altered microbiota and water transporter dysfunction in the colon. Consequently, the purgative effects of rhubarb may vary by patient.

In the present study, even when patients were so severely infected they experienced reflux of gastric juice, not only did the administration of rhubarb improve bowel movements, but it also decreased the reflux volume, suggesting an effect of rhubarb on the upper digestive tract. Recently, maintenance of intestinal motility has become an important issue in intensive-care medicine. Although drugs such as metoclopramide, erythromycin, neostigmine, and others are reported to resolve incompetent intestinal motility (25), there are problems with drug tolerance. Patients with feeding intolerance have lower numbers of total obligate anaerobes than do patients without feeding intolerance, which is associated with mortality (26). Such situations in which the continuous reflux of gastric juice prevents successful enteral nutrition can result in an unfavorable condition from the viewpoint of wound healing or immunodeficiency. A Japanese *kampo* medicine called *rikkunshito* has been found to be effective for treating such functional gastrointestinal disorders and is also reported effective for gastric juice reflux in intensive-care patients (27, 28). In our patients, the action of rhubarb to stimulate intestinal motility may also have worked on the upper digestive tract and thereby decreased gastric juice reflux. The gastric juice reflux observed in four of our patients stopped before enteral nutrition began. The mechanism underlying these effects is a subject for future investigation, but rhubarb may contain motile ingredients that act on the upper gastrointestinal system in addition to its laxative effect. Rhein anthrone or its combination with pre-existing motility drugs might attenuate drug tolerance. As a limitation of this study, we could not start treatment with the same timing in all cases because this is a retrospective case report, and the number of days of constipation before treatment differed among patients. Further prospective studies are needed to clarify the effects of rhubarb.

Improvement in intestinal motility can prevent sepsis of gut origin (29). Wan et al. reported that, in 126 patients with severe acute pancreatitis treated with enteral nutrition and rhubarb, the abdominal condition recovered relatively early, and the levels of plasma C-reactive protein and IL-6 were significantly decreased (30).

In conclusion, the present study suggested that rhubarb was useful for treating incompetent intestinal motility in patients with systemic inflammatory response syndrome. Further clinical studies of rhubarb are required to determine the indications and suitability of rhubarb as a new therapy for intestinal dysmotility and constipation in critically ill patients.

The authors state that they have no Conflict of Interest (COI).

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