Efficacy of Partially Hydrolyzed Guar Gum-Added Oral Rehydration Solution in the Treatment of Severe Cholera in Adults

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Abstract
Background: Partially hydrolyzed guar gum (PHGG) is a water-soluble fiber if added to oral rehydration solution (ORS) and undergoes fermentation in the colon liberating short chain fatty acids (SCFAs). SCFAs potentiate the effect of ORS, reducing the severity of diarrhea. ***Aim:*** To examine the effect of PHGG-added ORS in reducing the stool output and duration of diarrhea in adult cholera. ***Methods:*** 195 male patients were studied in a randomized controlled trial: (a) 65 received ORS + 25 g PHGG; (b) 65 received ORS + 50 g PHGG, and (c) 65 received ORS alone (control). Major outcomes were stool weight and duration of diarrhea. ***Results:*** No significant differences were found in mean ± SD stool weight (g/kg b.w.) during the first and second 24 h. In the subgroup analysis (excluding very high purging patients, stool weight in the first 24 h was >10 kg), the stool weight (g/kg b.w.) was significantly reduced in the first 24 h in both groups receiving PHGG (PHGG 25 g, 136 ± 68 vs. PHGG 50 g, 144 ± 49 vs. control, 176 ± 43, p = 0.01). ***Conclusion:*** PHGG-added ORS might have a beneficial effect in moderately purging adult cholera. However, further studies are warranted to confirm the preliminary findings.

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Introduction

Many of the effects of fiber on stool output arise from their degradation in the colon by resident bacterial flora. The main products of fiber fermentation are short-chain fatty acids (SCFAs) including acetate, propionate and butyrate, which represent the major anions in the colon [1]. Most of the SCFAs that are produced are likely to be absorbed by the colonic epithelium [2] and are metabolized in the epithelium (butyrate), the liver (propionate) or peripheral tissues (acetate). The transepithelial transport of SCFAs is associated with an increase of sodium absorption from the colon which results in increased water absorption from the lumen [3–5]. This effect may be particularly important in acute diarrheal diseases where increased purging and associated reduced food intake might deplete the colon of SCFAs leading to colonic dysfunction [6, 7]. Thus, luminal SCFA levels in the colon might influence the clinical course of acute diarrheal diseases. SCFAs have also been shown to be clinically important in transmissible gastroenteritis of swine [8], where animals infected with the virus develop acute enteritis with marked fluid loss. Young animals develop severe diarrhea as their colonic mucosa is incapable of absorbing fluid, whereas colonic absorption in older infected animals is increased by about 6-fold over the controls. This compensatory response prevents severe diarrhea for the production of SCFAs.

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Cholera is a disease of humans affecting the small intestine where fluid and electrolyte secretion is increased while their absorptions are decreased leading to profuse watery diarrhea. As the human colon has the capacity to absorb water and electrolytes [9], some compensation is expected to occur reducing the diarrheal loss. A recent study [10] has shown that SCFAs stimulate sodium absorption in the colon, an effect that is independent of cyclic AMP. Additionally, SCFAs have been shown to inhibit cyclic AMP-mediated chloride secretion in the colon [11]. The SCFA-enhanced colonic absorption of water and electrolytes might be exploited in the treatment of acute diarrheal diseases. Oral rehydration therapy (ORT) has dramatically changed the management of acute diarrheal disease. However, efforts are continuing for improving the efficacy of oral rehydration solution (ORS). Cereal-based ORSs have been shown to reduce the stool volume by about 30–40% in cholera compared to the WHO ORS [12, 13]. It is possible that, at least in part, their effect on stool volume reduction might be attributed to SCFAs produced by fermentation of unabsorbed carbohydrate, including dietary fiber in the colon.

The colonic epithelial cells utilize SCFAs as a source of energy for their various metabolic activities [14]. Human and animal colonocytes use butyrate in preference to glucose, glutamine or ketone bodies as fuel sources [14–17]. Thus, in contrast to small intestinal cells, colonic epithelial cells derive the major part of their energy supply from the lumen rather than from blood. Depriving luminal nutrition of the mucosa has been found to induce fluid secretion [18–20]. Recent clinical studies have demonstrated the beneficial effect of amylase-resistant starch in the treatment of adult cholera [21] and partially hydrolyzed guar gum (PHGG), a soluble fiber in the treatment of children with acute and persistent diarrhea [22, 23]. Furthermore, several studies [24–26] in the past have demonstrated that PHGG was effective in preventing diarrhea in patients with enteral nutrition after surgery and in critically ill patients. In this study, we evaluated the efficacy of PHGG-added ORS in reducing the severity and duration of adult cholera, a form of severe dehydrating diarrhea.

Subjects and Methods

The study was designed as a prospective, open, randomized, controlled clinical trial to evaluate the efficacy of PHGG-supplemented ORS in the treatment of severe cholera in adults in comparison with World Health Organization (WHO) recommended reduced osmolarity ORS (WHO ORS). The participants of this study were selected from among those attending the Dhaka Hospital of ICDDRB from January 2004 to December 2006. The Ethics Committee of the ICDDRB had approved the protocol, and written informed consent was obtained from each participant before their enrollment. Adult male patients aged 18–55 years with a history of watery diarrhea of <24 h and severe dehydration, and their initial stool dark-field microscopy positive for *Vibrio cholerae,* were eligible for participation in the study. Those with a history of chronic diarrhea, dysentery, renal or hepatic dysfunction, receiving antimicrobial or antidiarrheal drugs within 1 week prior to admission, and refusal to provide written informed consent, were excluded from the study. After initial screening, patients were taken to the research ward of Dhaka Hospital, weighed, and placed on a cholera cot. A standard medical history, thorough physical examination including assessment of dehydration using modified WHO guidelines [27] and vital signs were recorded in predesigned forms. The patient enrolment in the study was done from 06:00 to 14:00 h, 7 days a week. Prior to randomization, all patients were rehydrated with intravenous fluids containing polyelectrolytes (Na 133, Cl 98, K 13, and acetate equivalent to 48 mmol/l of bicarbonate) at a rate 100 ml/kg over 4–6 h, in addition an amount equivalent to their stool volume during this period.

Randomization

Eligible patients who completed rehydration (within 4–6 h of the observation period) were randomized in equal numbers to receive: (a) standard WHO ORS (Na 75, glucose 75, Cl 65, K 20, citrate 10 mmol/l, and osmolarity 245 mosm/l) + 25 g PHGG/l; (b) standard WHO ORS + 50 g PHGG/l, and (c) standard WHO ORS without PHGG. A randomization list was prepared for an intervention to control ratio 1:1:1 using a random number table with permuted blocks of 12 and compiled by a statistician not involved in the study. Serially numbered sealed identical envelopes were also prepared by the statistician containing the name of the allotted ORS. The envelopes were kept with the hospital's pharmacist. Upon enrolment, the requisition for ORS was given to the pharmacist indicating the serial number and patient's name. The pharmacist prepared the ORS accordingly and supplied it to the study nurse indicating the patient's name and serial number. The allocation of ORS could not be blinded because 50 g PHGG made a slight change in color of the solution, although the PHGG dissolves completely in ORS solution.

Case Management

Immediately after randomization (following intravenous rehydration), maintenance ORT was initiated using the assigned ORS solution. During the maintenance phase, patients consumed ORS solution according to need, but a minimum amount equal to watery/loose stool plus vomit. All study patients received oral doxycycline 300 mg as a single dose within 20 min of randomization. A standard local food was provided three times daily according to the hospital practice: breakfast (bread, egg, sugar) at 06:30 h, lunch (boiled rice, meat/fish, lentil soup) at 12:00 h and supper (food as at lunch) at 18:00 h. Plain water was allowed as desired by the patients preferably after food. Intravenous fluid therapy was restarted in some patients developing signs of severe dehydration despite appropriate ORS therapy or/and for excessive vomiting that prevented successful oral therapy. Stools were collected in a bucket placed underneath the cholera cot. All intakes (intravenous fluid, ORS, water) and outputs (stool, urine, vomit)

Table 1. Admission clinical characteristics of the study patients

Variables	WHO ORS + PHGG (25 g) (n = 65)	WHO ORS + PHGG (50 g) (n = 65)	WHO ORS alone (n = 65)	p value
Age, years	29 ± 10	29 ± 8	29 ± 9	0.27
Admission b.w., kg	45 ± 6	46 ± 5.6	46.5 ± 7	0.51
Duration of diarrhea before admission, h	8.8 ± 4	9 ± 4.5	9 ± 5	0.88
Number of stools before admission in the last 24 h	15 ± 8	12 ± 7	14 ± 11	0.11
Duration of vomiting, h	6 ± 4	6 ± 4.4	6 ± 3.7	0.81
Number of vomits before admission in the last 24 h	8 ± 7	6 ± 4	8 ± 7	0.07
Initial intravenous fluid, ml/kg b.w.	159 ± 33	159 ± 35	150 ± 27	0.21
Stool weight before randomization, g/kg b.w.	38 ± 23	39 ± 24	41 ± 21	0.69

Values are mean ± SD. b.w. = Body weight.

were measured and recorded for every 6-hour period of the study. Stool weight was measured with an electronic scale with a precision of 1 g (Sartorius, Göttingen, Germany). During the time of intake and output measurement, nurses also recorded the consistency of stool (watery, soft or formed). Urine was separated in a urine collector and the volume measured with a calibrated glass cylinder. The weight of vomit was measured by collection in a preweighed bowl by subtracting that from the final weight of the bowl. The volume of ORS and plain water (ml) consumed by the patients were measured with a calibrated cylinder. Body weight was measured on admission (before initiation of intravenous therapy) at randomization (after intravenous rehydration) and every 6 h until discharged, using the same electronic scale.

Laboratory Investigations
Fresh stool samples were examined for the presence of *V. cholerae* by dark-field microscopy during the 4- to 6-hour observation period. Stool samples were cultured for isolation and identification of *V. cholerae, Salmonella* and *Shigella* using the standard techniques. Peripheral venous blood samples were tested for hematocrit, total and differential white blood cells, blood urea nitrogen, creatinine, serum sodium, potassium, chloride, and bicarbonate at randomization and 24 h after randomization.

All patients were observed closely until discharge. Resolution of diarrhea was defined if patients did not have stool for at least 12 h or if they had two consecutive normal (formed) stools. Clinical success was defined as cessation of diarrhea within 72 h from the start of study medication, and those with continued watery stool for >72 h were considered as clinical failure. Oral therapy failure was defined as reappearance of signs and/or symptoms of dehydration, requiring unscheduled intravenous fluid therapy. Duration (h) of diarrhea was calculated from the time of randomization to the last watery stool.

Statistical Methods
Sample size was determined based on a 30% expected reduction in the stool output in either of the two groups of patients to be treated with PHGG-added WHO ORS compared to the control group of patients who would be treated with the standard WHO ORS. In a recent study [28], the mean ± SD stool (g/kg/1st 24 h) in cholera patients was observed to be 273 ± 157. To demonstrate a 30% reduction in the stool volume, at 5% significance level with a power of 80%, 58 patients would be required in each of the three treatment groups. To adjust for a 10% dropout due to any reason, 64 patients would be required to be enrolled in each group. In fact, 65 patients in each group were studied.

Data Analysis
Statistical analyses were performed using SPSS PC+ (Version 10). All statistical tests were two-tailed, performed at 5% level of significance. Continuous variables were compared using the analysis of variance (ANOVA) for within-group comparison and the post-hoc test was used for multiple comparisons. Categorical variables were compared with the χ^2 test or Fisher's exact test as appropriate. Kaplan-Meier survival curves were constructed for the duration of diarrhea and compared by the log-rank test.

Results

In total, 367 patients were screened for eligibility. Of these, 195 were randomized for inclusion in the study: 65 received WHO ORS + 25 g PHGG; 65 received WHO ORS + 50 g PHGG, and 65 received WHO ORS without PHGG (control). 174 patients were excluded because stool for dark-field examination at admission was negative for *V. cholerae* (159 patients) or refusal of informed consent (13 patients). Clinical characteristics at admission such as admission body weight, age of the patients, duration of diarrhea, duration of vomiting, number of stools before admission, number of vomits before admission, initial requirement of intravenous fluid for rehydration and stool output during the screening period were comparable among the three treatment groups (table 1). Comparison of stool output during the first and second 24 h after randomization revealed no significant difference among the treatment groups. Similarly, intake of ORS during these

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Table 2. Comparison of outcome variables

Variables	WHO ORS + PHGG (25 g) (n = 65)	WHO ORS + PHGG (50 g) (n = 5)	WHO ORS alone (control) (n = 65)	p value
Stool weight, 1st 24 h, g/kg b.w	225 ± 127	255 ± 115	234 ± 111	0.18
Stool weight, 2nd 24 h, g/kg b.w.	52 ± 74	73 ± 84	57 ± 81	0.14
Urine volume, 1st 24 h, ml/kg b.w.	99 ± 48	94 ± 48	111 ± 49	0.14
Urine volume, 2nd 24 h, ml/kg b.w.	120 ± 38	119 ± 45	109 ± 33	0.58
ORS, 1st 24 h, ml/kg b.w.	282 ± 115	304 ± 119	286 ± 80	0.46
ORS, 2nd 24 h, ml/kg b.w.	84 ± 59	109 ± 89	80 ± 78	0.06
Water intake, 1st 24 h, ml/kg b.w.	62 ± 33	63 ± 26	61 ± 32	0.81
Water intake, 2nd 24 h, ml/kg b.w.	84 ± 49	90 ± 33	71 ± 42	0.25
Duration of diarrhea after randomization, h	31.44 ± 11.1	36.9 ± 14.3	32 ± 12.5	0.04*
Patients who received unscheduled i.v. therapy	16/65 (25)	8/65 (12)	11/65 (17)	0.161

Values are mean $\pm$ SD or numbers (%). b.w. = Body weight.
* p value from ANOVA (comparison within three groups). Multiple comparisons (post-hoc test): PHGG 25 g vs. control, p = 0.97; PHGG 50 g vs. control, p = 0.09; PHGG 25 g vs. PHGG 50 g, p = 0.06.

Table 3. Comparison of outcome variables (subgroup analysis) excluding very high purging patients (1st 24 h stool weight >10 kg)

|	WHO ORS + PHGG (25 g) (n = 34)	WHO ORS + PHGG (50 g) (n = 24)	WHO ORS alone (control) (n = 38)	p value
Stool weight, 1st 24 h, g/kg b.w.	136 ± 68	144 ± 49	176 ± 43	0.01*
Stool weight, 2nd 24 h, g/kg b.w.	17 ± 21	22 ± 20	20 ± 34	0.79
ORS, 1st 24 h, ml/kg b.w.	213 ± 66	216 ± 93	247 ± 58	0.14
ORS, 2nd 24 h, ml/kg b.w.	28 ± 38	29 ± 36	26 ± 39	0.79

Values are mean $\pm$ SD. b.w. = Body weight.
* p value from ANOVA (within group comparison). Multiple comparisons (post-hoc tests): PHGG 25 g vs. control, p = 0.004; PHGG 50 g vs. control, p = 0.003; PHGG 25 g vs. PHGG 50 g, p = 0.56.

periods also showed no difference among the groups (table 2). When a subgroup analysis excluding very high purging (stool weight >10 kg during the first 24 h) patients was performed, the stool weight was significantly reduced in the groups receiving either ORS with 25 g PHGG/l (PHGG 25 g vs. control, p = 0.004) or ORS with 50 g PHGG/l (PHGG 50 g vs. control, p = 0.003) compared with the ORS without any PHGG (table 3). Intake of ORS was also reduced in these patients; however, the differences were not statistically significant (table 3). The mean duration of diarrhea was similar in the groups receiving WHO ORS with 25 g/l PHGG and WHO ORS without any PHGG; however, the mean duration was prolonged for a few hours in the group receiving WHO ORS with 50 g/l PHGG (table 2). Although the difference was significant marginally for within-group comparison (p =

0.04), multiple comparisons (post-hoc tests) failed to show a statistical significance (PHGG 25 g vs. control, p = 0.97; PHGG 50 g vs. control, p = 0.09; PHGG 25 g vs. PHGG 50 g, p = 0.06). That might explain why comparison of survival analysis for duration of diarrhea (fig. 1) demonstrated no statistically significant difference (p = 0.12, log-rank test).

Discussion

The results of the study demonstrate that PHGG added to glucose-based ORS has shown beneficial effect in terms of reducing the stool output in patients with moderate severity of diarrheal illness (after exclusion of very high purging patients, although it was not planned ini-
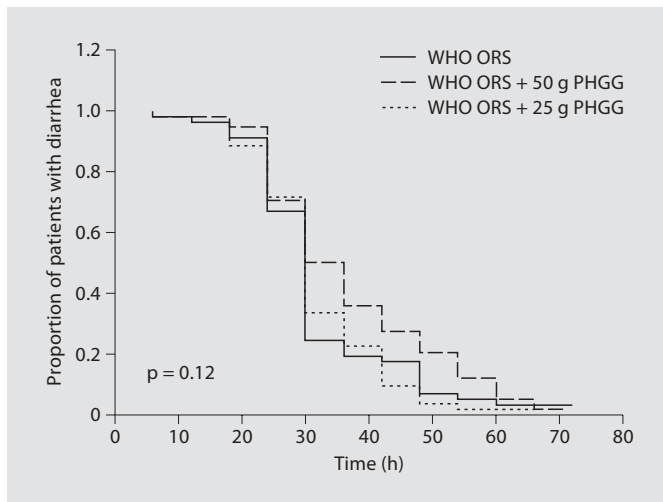
Fig. 1. Kaplan-Meier survival plot for the duration of diarrhea.

tially). However, PHGG-containing ORS has failed to show a beneficial effect during treatment of severe adult cholera with very high stool output (>10 kg in the first 24 h). This failure may be explained as: (a) the transit time in high purging cholera patients is very short, causing a washout effect leaving little time for fermentation; (b) the high purging patients required an increased amount of ORS including the fiber, and unabsorbed fiber added some weight to stool, and (c) in addition, the unfermented fiber might hold some water which subsequently led to an increased stool weight. This mechanism would also be consistent with the failure of exhibiting a beneficial effect using ORS containing 50 g PHGG/l in the treatment of moderately purging patients that it could prolong diarrhea. Based on a similar hypothesis, Ramakrishna et al. [21] have carried out a study using glucose ORS supplemented with amylase-resistant starch in the treatment of adolescent and adult cholera. The addition of amylase-resistant starch significantly reduced the duration of diarrhea and stool weight after 12 h; however, the severity of diarrhea in patients (mean stool weight <10 kg) of that study was less than the present study, and the sample size was very small (16 patients in each group). Recently published results of two studies [22, 23] that reported a beneficial effect of PHGG added to ORS or diet in the treatment of non-cholera diarrhea in children also substantiate the findings of our present study.

In cholera, the reserve capacity of the colon is impaired [7]. SCFAs are a potent stimulus for the colonic absorption of sodium and water from both the normal and se-

creting colon [2, 29, 30]. The availability of SCFAs depends on the fermentation of unabsorbed carbohydrate in the colon. Whether fermentation of unabsorbed PHGG was decreased due to a washout effect in very high purging patients cannot be answered from this study because measurement of luminal SCFAs was not performed. It has been demonstrated in an earlier study [31] that PHGG added to liquid diet slows colonic transit time in healthy volunteers that might help in fermentation of PHGG for the prolongation of retaining time in the colon; however, it might not happen in very severe cholera. Another factor that is related to fermentation of unabsorbed carbohydrates in the colon is the availability of colonic flora; the washout effect in very high purging patients might have led to a decrease of colonic flora needed for fermentation of unabsorbed carbohydrate and formation of SCFAs.

In spite of intake of large doses of PHGG and very high purging in adult cholera patients, no adverse effects such as vomiting, abdominal distension, etc. were noted in this study except prolongation of diarrhea for several hours with PHGG (50 g/l). As PHGG (25 g/l) in ORS has shown a better effect, further lowering the dose to 10–15 g/l might be tried in future studies to establish the optimum dose of PHGG.

In conclusion, PHGG-supplemented ORS might be beneficial in moderately severe purging adult cholera patients. Further studies are warranted to confirm and substantiate the present study findings.

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