

AMYLASE-RESISTANT STARCH PLUS ORAL REHYDRATION SOLUTION FOR CHOLERA

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ABSTRACT

Background Although standard glucose-based oral rehydration therapy corrects the dehydration caused by cholera, it does not reduce the diarrhea. Short-chain fatty acids, which are produced in the colon from nonabsorbed carbohydrates, enhance sodium absorption. We conducted a study to determine the effects of an orally administered, nonabsorbed starch (i.e., one resistant to digestion by amylase) on fecal fluid loss and the duration of diarrhea in patients with cholera.

Methods We randomly assigned 48 adolescents and adults with cholera to treatment with standard oral rehydration therapy (16 patients), standard therapy and 50 g of rice flour per liter of oral rehydration solution (16 patients), or standard therapy and 50 g of high-amylose maize starch, an amylase-resistant starch, per liter of oral rehydration solution (16 patients). The primary end points were fecal weight (for every 12-hour period during the first 48 hours after enrollment) and the length of time to the first formed stool.

Results The mean (\pm SD) fecal weights in the periods 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after enrollment were significantly lower in the resistant-starch group (2206 ± 1158 g, 1810 ± 1018 g, and 985 ± 668 g) than in the standard-therapy group (3251 ± 766 g, 2621 ± 1149 g, and 2498 ± 1080 g; $P=0.01$, $P=0.04$, and $P=0.001$, respectively). From 36 to 48 hours after enrollment, fecal weight was also significantly lower with the resistant-starch therapy than with the rice-flour therapy (985 ± 668 g vs. 1790 ± 866 g, $P=0.01$). The mean duration of diarrhea was significantly shorter with the resistant-starch therapy (56.7 ± 18.6 hours) than with standard therapy alone (90.9 ± 29.8 hours, $P=0.001$) or the rice-flour therapy (70.8 ± 20.2 hours, $P=0.05$). Fecal excretion of starch was higher with the resistant-starch therapy (32.6 ± 30.4) than with the standard therapy (11.7 ± 4.1 g, $P=0.002$) or the rice-flour therapy (15.1 ± 8.4 g, $P=0.01$).

Conclusions The addition of a resistant starch to oral rehydration solution reduces fecal fluid loss and shortens the duration of diarrhea in adolescents and adults with cholera. (N Engl J Med 2000;342:308-13.)

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DIARRHEAL disease is one of the two main causes of death in children in developing countries, claiming the lives of more than 3 million children every year.¹ In controlled studies, oral rehydration therapy is very effective in correcting dehydration and reducing mortality.² Glucose and other solutes stimulate the absorption of sodium from the small intestine, a process that is

not inhibited by cyclic nucleotides that modify processes for the active transport of sodium and chloride.³

The rate of use of oral rehydration therapy has remained low in both developing and developed countries, even though it has been publicized through health-education efforts.⁴⁻⁷ In developing countries, several factors are responsible for the poor acceptance of oral rehydration therapy. There is a perception that oral rehydration is not effective because it does not reduce the manifestations of diarrhea, such as the loss of fluid in feces, or the duration of diarrheal illness.^{8,9} The glucose-based oral rehydration solution recommended by the World Health Organization may, paradoxically, increase fecal fluid loss.¹⁰ Because of these limitations, there has been a substantial impetus to develop a better oral rehydration therapy.¹¹

The colon absorbs sodium against steep electrochemical gradients and can absorb up to about 5 liters of fluid daily.¹² The absorptive capacity of the colon can compensate, to a considerable extent, for the secretion of fluid from the small intestine in diarrheal disease.¹³ In cholera, in addition to such secretion, there is decreased absorption of fluid in the large intestine,¹⁴ a phenomenon that can be reversed by short-chain fatty acids.¹⁵ Short-chain fatty acids are produced in the colon by the bacterial fermentation of unabsorbed carbohydrates.¹⁶ Starch that is resistant to digestion by amylases in the small intestine (amylase-resistant starch) is found in small quantities in many cereals and is a good substrate for colonic fermentation.^{16,17} High-amylose maize starch, obtained from a specific variety of corn, is rich in resistant starch that is type 2, a classification based on the structure and conformation of native starch molecules.¹⁷ When it is eaten uncooked, 50 to 70 percent of the starch is not digested in the small intestine.¹⁸ In healthy humans, high-amylose maize starch is fermented and converted to short-chain fatty acids in the colon.^{18,19}

Because amylase-resistant starch usually is fermented in the colon and is converted to short-chain fatty acids, and because the stimulation of sodium absorption by short-chain fatty acids has not been altered by mucosal cyclic AMP experimentally,²⁰ we hypoth-

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esized that adding amylase-resistant starch to the treatment given to patients with cholera would result in reduced fecal volume and a shorter duration of diarrhea. We undertook the present study to test this hypothesis.

METHODS

Patients

Forty-eight consecutive adolescent or adult patients (age range, 14 to 58 years) with cholera who were admitted to the Christian Medical College and Hospital in Vellore, India, between May 1994 and July 1996 entered the study. Patients were included if they had acute, watery diarrheal illness of less than 72 hours' duration and were positive for organisms associated with cholera by hanging-drop examination of the stool. (In hanging-drop examination, a wet mount of stool under dark-field illumination is examined for organisms with a motility pattern characteristic of vibrios.) Patients who had previously received antibiotic therapy and those with severe systemic illness were excluded from the study.

Study Protocol

We randomly assigned patients to receive one of three therapies: a glucose-based oral rehydration solution (World Health Organization formula B), a glucose-based oral rehydration solution to which 50 g of rice flour was added per liter of solution, or a glucose-based oral rehydration solution to which 50 g of high-amylose maize starch was added per liter of solution (amylase-resistant starch). The randomization involved the use of permuted blocks in each of which six patients were randomly assigned to the three treatment groups so that two patients were in each treatment group. We then chose a new block of six patients, so that the sequence of assignment to the treatment groups was different from the previous block, until we had assigned eight blocks of patients.

Both the rice flour (obtained commercially) and the amylase-resistant starch (provided by Starch Australasia, Sydney, Australia) formed finely dispersed suspensions, which were ingested immediately after preparation. The glucose-based oral rehydration solution was packaged in bags, each of which could be reconstituted in 200 ml of water. The amylase-resistant starch and rice flour were added in 10-g quantities, uncooked, to 200 ml of reconstituted oral rehydration solution just before consumption. The osmolality of the three solutions was similar and averaged 327 mOsm per kilogram as measured by a vapor-pressure osmometer (Wescor, Logan, Utah). All patients provided oral informed consent. The study protocol was approved by the research committee of the Christian Medical College and Hospital.

Patients were treated with oral rehydration solution (alone or with rice flour or amylase-resistant starch added) according to World Health Organization treatment plan B, which is used for the management of mild to moderate dehydration and involves the administration of oral rehydration solution at a rate of 75 ml per kilogram of body weight (to a maximum of 4 liters) in the first four hours. Rice flour, a common constituent of cereal-based oral rehydration solutions, contains both starch and other complex carbohydrates. Because of the nature of the suspension formed with amylase-resistant starch, patients could not be made completely unaware of the treatment they received. However, rice flour and amylase-resistant starch formed suspensions of similar appearance, and patients and their care givers did not know whether the patients were assigned to the rice-flour group or the resistant-starch group. Patients were allowed to drink additional water without restriction. Patients who had hypotension at presentation were rehydrated intravenously over a period of four hours and then enrolled in the study. A standard southern Indian vegetarian diet was provided to all patients, who were encouraged to eat as soon as possible. A 300-mg dose of doxycycline was administered orally after 24 hours.

All feces from each patient were collected in buckets lined with plastic bags and stored at 4°C. Twice a day, the collected feces were weighed, and aliquots were taken and stored at -20°C until

analysis. The collection, weighing, and analysis of the feces were carried out by one of the investigators, who was unaware of the treatment that the patient was receiving. Fluid intake and urine output were monitored every six hours. Serum electrolytes, urea nitrogen, and creatinine were measured daily. Fecal collection was continued for 48 hours, and patients were hospitalized until the consistency of the stool returned to normal. Stool consistency was graded as watery, semi-loose, semi-formed, mushy, or solid. The timing of each stool was noted. The duration of diarrhea was arbitrarily defined as the period from the start of oral hydration until the first mushy or formed stool.

Transit and Fermentation Studies

In six additional patients with cholera, 1 liter of oral rehydration solution with glucose that contained 50 g of amylase-resistant starch and 2 g of polyethylene glycol with an average molecular weight of 4000 (PEG 4000, Fluka, Buchs, Switzerland) was instilled into the stomach through a nasogastric tube. All feces were collected and monitored for the presence of polyethylene glycol, glucose, and starch. The patients received fluids intravenously and were not permitted to eat or drink for 12 hours. After 12 hours, patients again received therapy with oral hydration and were permitted to eat and drink.

Chemical and Biochemical Analyses

Fecal starch was measured enzymatically with a starch-assay kit (Total Starch Assay Procedure, Megazyme, Warriewood, Australia). Fecal glucose was measured enzymatically with glucose oxidase. Fecal polyethylene glycol was measured by turbidimetry.²¹

Statistical Analysis

All values are expressed as means ±SD. We measured the significance of differences between groups using two-sample t-tests or Mann-Whitney U tests, as appropriate. All P values are two-tailed. P values of 0.05 or less were considered to indicate statistical significance.

RESULTS

Patients enrolled in the three groups did not differ significantly with regard to demographic characteristics (Table 1). None of the patients in the study had coexisting medical illness, except one assigned to standard therapy, who had extrahepatic portal hypertension with no history of gastrointestinal bleeding or evidence of ascites or liver dysfunction. All patients enrolled completed the study.

Fecal Weight

Table 2 lists the mean fecal weight in the three treatment groups during four consecutive 12-hour

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	STANDARD-THERAPY GROUP (N = 16)	RICE-FLOUR GROUP (N = 16)	RESISTANT-STARCH GROUP (N = 16)
Age (yr)			
Mean	36.4	37.4	33.9
Range	16-54	14-58	15-54
Sex (M/F)	12/4	10/6	11/5
Pathogen (no.)			
<i>Vibrio cholerae</i> O1	13	12	13
<i>Vibrio cholerae</i> O139	3	4	3

TABLE 2. FECAL WEIGHT AFTER THE ADDITION OF RICE FLOUR AND AMYLASE-RESISTANT STARCH TO STANDARD ORAL REHYDRATION SOLUTION.*

PERIOD AFTER ENROLLMENT	FECAL WEIGHT			P VALUE		
	STANDARD-THERAPY GROUP (N=16)	RICE-FLOUR GROUP (N=16)	RESISTANT-STARCH GROUP (N=16)	STANDARD THERAPY VS. RICE FLOUR	STANDARD THERAPY VS. RESISTANT STARCH	RICE FLOUR VS. RESISTANT STARCH
	grams					
0-12 hr	3889±1275	3679±1195	3938±2046	0.64	0.94	0.67
12-24 hr	3251±766	2869±735	2206±1158	0.16	0.01	0.06
24-36 hr	2621±1149	2186±899	1810±1018	0.24	0.04	0.28
36-48 hr	2498±1080	1790±866	985±668	0.05	0.001	0.01

*Plus-minus values are means ±SD.

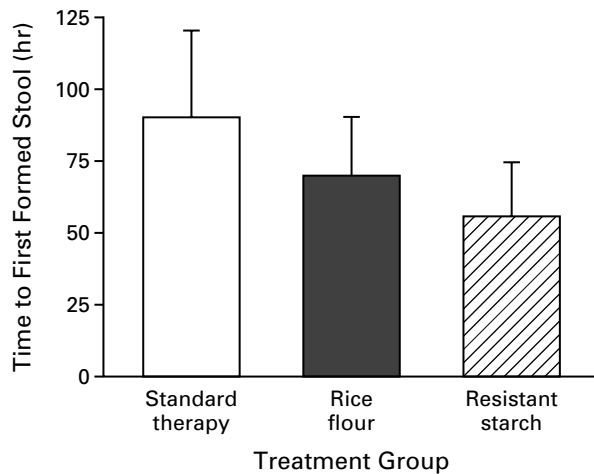


Figure 1. The Effect on the Time to the First Formed Stool of Adding Rice Flour and Resistant Starch to Standard Oral Rehydration Solution.

The values shown are means (±SD) for 16 patients in each group. Stool consistency was characterized as watery, semi-loose, semi-formed, mushy, or solid. A formed stool was defined as either mushy or solid. The time to the first formed stool was significantly shorter in the resistant-starch group than in the standard-therapy group (P=0.001) or the rice-flour group (P=0.05), and it was significantly shorter in the rice-flour group than in the standard-therapy group (P=0.03).

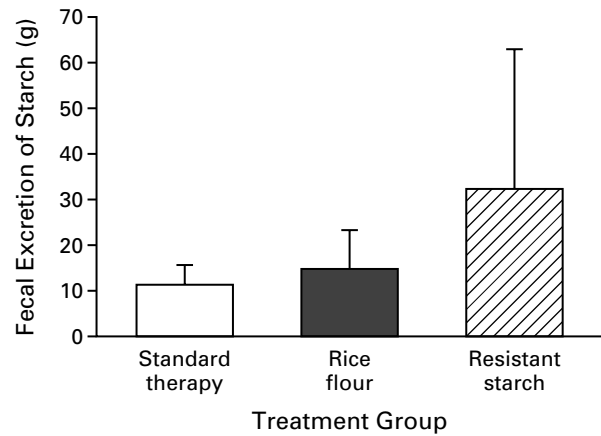


Figure 2. The Effect on Fecal Starch Excretion of Adding Rice Flour and Resistant Starch to Standard Oral Rehydration Solution.

The values shown are means (±SD) for 16 patients in each group. The amounts of fecal starch excreted are the sums of four 12-hour periods. Excretion was significantly higher in the resistant-starch group than in the standard-therapy group (P=0.002) or the rice-flour group (P=0.01).

periods that began at enrollment. Fecal weight during the periods from 0 to 12 hours, 12 to 24 hours, and 24 to 36 hours after enrollment for patients treated with the rice-flour therapy was not significantly different from that for patients treated with standard therapy. However, during the period from 36 to 48 hours, fecal weight was significantly lower in the rice-flour group than in the standard-therapy group (P=0.05). In the resistant-starch group, the fecal weight was similar to that in the other two groups in the first 12 hours but was significantly lower than the

weight in the standard-therapy group during the periods from 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after enrollment and was significantly lower than that in the rice-flour group during the 36-to-48-hour period.

Time to the First Formed Stool

The length of time to the first formed stool was a mean of 90.9±29.8 hours among the patients treated with standard therapy but was significantly shorter among the patients in the rice-flour group (70.8±

TABLE 3. CUMULATIVE FECAL RECOVERY OF POLYETHYLENE GLYCOL AND STARCH FROM SIX ADDITIONAL PATIENTS IN WHOM 1 LITER OF ORAL REHYDRATION SOLUTION THAT CONTAINED 50 g OF RESISTANT STARCH AND 2 g OF POLYETHYLENE GLYCOL WAS INSTILLED INTO THE STOMACH.*

SUBSTANCE	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr	6 Hr	12 Hr
Polyethylene glycol (g)	0.1±0.1	0.2±0.2	0.6±0.2	1.1±0.1	1.5±0.1	1.7±0.1	1.9±0.2
Starch (g)	0.1±0.0	0.1±0.1	1.8±1.8	3.2±3.2	5.9±6.6	7.4±8.0	8.3±8.9

*The values shown are means ±SD.

20.2 hours, $P=0.03$). The time to the first formed stool in the resistant-starch group (56.7 ± 18.6 hours) was significantly shorter than in either the standard-therapy group ($P=0.001$) or the rice-flour group ($P=0.05$) (Fig. 1).

Fecal Starch

The total amount of starch excreted in feces over a period of 48 hours was significantly higher in the resistant-starch group (32.6 ± 30.4 g) than in either the standard-therapy group (11.7 ± 4.1 g, $P=0.002$) or the rice-flour group (15.1 ± 8.4 g, $P=0.01$) (Fig. 2). Glucose was recovered in only negligible quantities from the feces in all groups, and the amount did not differ significantly between the groups.

Transit of Starch from Stomach to Stool

As shown in Table 3, total fecal recovery of polyethylene glycol was 95 ± 10 percent, and none was recovered after 12 hours. After the instillation of amylase-resistant starch into the stomach, substantial quantities were recovered from feces, an average of 16.6 percent of the amount instilled. Free glucose was recovered in negligible quantities.

DISCUSSION

There have been many attempts to improve the characteristics of oral rehydration solution so that it reduces fecal fluid loss and the duration of diarrhea. Most attempts have focused on the enhancement of small-bowel absorption of fluids through the use of amino acids or hypo-osmolar solutions.¹¹ In the present study, we took a different approach: we tested whether the addition of ingredients that improved colonic absorption (without altering osmolality) would reduce the output of stools and the duration of diarrhea in adolescent and adult patients with cholera. Our findings indicate that the duration of diarrhea was significantly shortened, and the loss of fluid in stools considerably reduced, when resistant starch was administered in addition to the standard oral rehydration solution and when patients were encouraged to eat as soon as possible after the administration of the solution.

The use of cereal-based oral rehydration therapy

in patients with cholera²² and rice-derived glucose polymer in infants with diarrhea (predominantly those with rotavirus infection)²³ significantly reduced stool output. These clinical benefits stem from the increased absorption of sodium and water.¹¹ Although the hypo-osmolality of cereal-based solutions has been considered critical to the absorption of sodium and water,¹¹ other possible factors include a kinetic advantage of such solutions that results from the juxtaposition of hydrolytic and absorptive sites in the small intestine, enhancement of mucosal repair by luminal nutrients, and a specific antisecretory factor in rice. It is possible that some of these effects may contribute to the benefit of amylase-resistant starch, because some of the starch is digested in the small intestine.

Not considered in previous explanations of the efficacy of cereal-based oral rehydration therapy in reducing fecal fluid loss was the possibility of enhanced colonic absorption through the formation of short-chain fatty acids.²⁴ The ability of the colon to absorb sodium against substantial electrochemical gradients and its considerable reserve capacity to absorb fluid are important determinants of fluid loss from diarrhea.¹³ In cholera, the reserve capacity of the colon is impaired.¹⁴ Short-chain fatty acids are a potent stimulus for the colonic absorption of sodium and water from both the normal and the secreting colon.²⁵⁻²⁷ Sodium absorption that is linked to short-chain fatty acids is not inhibited by cyclic nucleotides²⁰ and is up-regulated by the action of cholera toxin in the colons of laboratory animals.²⁸ Thus, such sodium absorption from the colon is analogous to glucose-linked sodium absorption from the small intestine, which is also up-regulated by cyclic nucleotides.²⁹

Cereals contain complex carbohydrates classified as either nonstarch polysaccharides or starch.¹⁶ The starch in cereals is only partly digested in the small bowel; the proportion that is resistant to digestion depends on genetic factors (as in high-amylose maize) as well as physical aspects of the cooking and processing.¹⁷ When starch enters the colon, it is rapidly fermented, resulting in a higher proportion of butyrate relative to other short-chain fatty acids than is the case with other fermentation substrates.³⁰ Bu-

tyrate is the most effective of the three most abundant short-chain fatty acids in stimulating sodium absorption in the colon.²⁶

In the present study, the decreases in fecal weight and the time to the first formed stool that resulted from resistant-starch therapy were probably the result of fermentation of the resistant starch by colonic bacteria, with conversion to short-chain fatty acids, which then enhanced absorption of fluids and electrolytes in the colon. The excretion of fecal starch was significantly higher in patients who received the resistant-starch therapy than in patients who received the rice-flour or standard therapy.

On average, only 16.6 percent of a bolus dose of resistant starch administered in the stomach was recovered in the feces. Because more than 50 percent of uncooked amylase-resistant starch is resistant to digestion, it appears likely that more than 50 percent of the starch that reached the colon was metabolized to short-chain fatty acids, which were rapidly absorbed by colonic epithelial cells. Because neither the concentration nor the output of short-chain fatty acids in feces necessarily reflects their production, it is difficult to estimate production. In the present study, between 24 and 36 hours after enrollment, concentrations of short-chain fatty acids in feces were higher with resistant-starch therapy (16.2 ± 11.8 mEq) than with standard therapy (8.0 ± 10.2 mEq, $P=0.04$) or rice-flour therapy (8.0 ± 8.0 mEq, $P=0.03$). This increase may result, in part, from reduced fecal excretion of water. However, the total fecal output of short-chain fatty acids during the third and fourth 12-hour periods of the study showed a trend toward greater output in the resistant-starch group (64.5 ± 56.7 mEq) than in the standard-therapy group (35.0 ± 19.6 mEq, $P=0.06$) and the rice-flour group (35.9 ± 19.6 mEq, $P=0.07$).

The use of oral rehydration solution, along with the encouragement of patients to begin eating as soon as possible, is highly effective for correcting fluid and electrolyte losses in diarrhea. However, many factors have impeded the widespread acceptance of oral rehydration therapy, including the fact that there is continued fecal fluid loss and continued diarrhea after this therapy begins.^{8,9} The present study shows that in adolescent and adult patients with cholera, resistant starch, when added to oral rehydration solution, can successfully reduce fecal fluid loss and shorten the duration of diarrhea. Caution must be used in extrapolating the results for cholera to noncholera diarrhea, however. A meta-analysis of studies of cereal-based oral rehydration solutions showed that these solutions reduced fecal volume by 32 to 36 percent in patients with cholera, but only by about 18 percent in patients with diarrhea not caused by cholera.²² It is possible that the incorporation of substrate into oral rehydration solutions to promote fermentation in the colon would decrease fecal volume and the duration of illness in diarrhea not associated with

cholera. Such a solution could then be used universally for most diarrheal diseases.

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