SUCROSE OR GLUCOSE: WHICH SUGAR TO USE IN ORAL REHYDRATION SOLUTION? A SUMMARY OF FOUR CLINICAL TRIALS

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The question of the efficacy of a sucrose electrolyte solution in maintaining hydration in patients with acute diarrheal disease is a crucial one for health planners. Although sucrose electrolyte solution has been shown to be effective in several studies(1,2,3), including a double blind study by Palmer *et al.*(4), there has still been concern that a solution using sucrose is not as effective as one using glucose, that more patients will fail if sucrose is used, that purging rates will be increased and patients may drink excess quantities of the sucrose containing fluid. Sucrose, however, has the advantage of being cheaper and more available in most countries and these economic and distribution considerations are major constraints on the present use of oral solution.

A further question concerning oral therapy has arisen regarding rotavirus diarrhea, a major cause of infantile diarrhea throughout the world. In this disease, not only are intestinal disaccharidases decreased, but glucose facilitated transport is also defective in the involved mucosa(5) so there has been doubt as to the efficacy of either oral solution in viral diarrhea.

We therefore conducted a series of three double blind controlled trials of sucrose with glucose oral solution in patients hospitalized with bacterial and viral dehydrating diarrhea, and one "before-after" trial in children with rotavirus diarrhea attending the Matlab rehydration center.

Table 1 shows the four groups of patients studied at the Cholera Research Laboratory during the last year. The first group included 148 adult males with cholera-like diarrhea with at least 7.5% dehydration. The second group included 111 children with cholera-like diarrhea with at least 7.5% dehydration. These first two groups were studied during the 1977 fall cholera epidemic. The third group included 89 children with "rotavirus-like" diarrhea with some detectable dehydration. This group was studied during the winter 1978 rotavirus epidemic.

The final group of patients were made up of 787 children with rotavirus diarrhea who come to the Matlab rehydration unit during a time that rotavirus surveillance was being maintained. On a given day, the oral solution was switched from glucose to sucrose without informing the attendants who administered treatment.

I will first describe the methods and results of the double blind studies.

Patients were selected for these studies on clinical grounds of dehydration due to acute watery diarrhea. Patients with severe malnutrition or other systemic diseases were excluded. Patients were admitted directly to the clinical research ward where they were weighed, examined, placed on cholera

Table 1. Sucrose vs Glucose Oral Therapy Studies Done at CRL During 1977-1978

Double Blind Controlled Studies

1. 148 Adult males with cholera-like diarrhea and >7.5% dehydration.
2. 111 Children, age 5 mths - 4 yrs, with cholera-like diarrhea and >7.5% dehydration.
3. 57 Children, age 5 mths - 2-1/2 yrs, with rotavirus diarrhea and >5.0% dehydration.

"Before-After" Study

4. 787 Children, <5 yrs, with rotavirus diarrhea.

and initial specimens were obtained. The patients were stratified according to degree of dehydration and then randomized to either the glucose or sucrose treatment. Randomization was accomplished by drawing from an envelope, one of four letters (A,B, C,D) which corresponded to one of four solutions, two of which contained glucose and two of which contained sucrose. Four, rather than two solutions were used to protect the double blind nature of the study. All cholera patients were treated with tetracycline.

Moderately severe patients were scheduled to receive both rehydration and maintenance therapy by the oral route. Severely dehydrated patients were scheduled to receive 70% of their estimated deficit by the intravenous route and the remainder of their rehydration and all maintenance by the oral route. Failures were defined as those patients requiring any unscheduled intravenous fluid.

The oral solutions used contained the WHO formula(6) of salts plus either glucose 20 grams per liter or sucrose 40 grams per liter plus orange flavoring and coloring.

Table 2. Admission Characteristics of Adult Cholera-like Patients

	Sucrose Group		Glucose Group	
Number	75		73	
Mean Age (yrs)	31±1*		30±1	
Duration of diarrhea prior to admission (hrs)	12±1		12±1	
No. with 10% dehydration	51	(68%)	45	(62%)
Mean serum specific gravity	1.035		1.035	
Mean serum bicarbonate	17.0		16.7	
Enteric pathogens isolated:				
V. cholerae	36	(48%)	43	(59%)
Enterotox. *E. coli* (without *V. cholerae*)	27	(36%)	24	(33%)
No pathogen	8	(11%)	5	(7%)

* Mean ± Standard Error.

Laboratory specimens were obtained for serum chemistries, stool electrolytes and stool reducing substances before and after acid hydrolysis (7). A stool specimen was cultured for pathogenic bacteria including enterotoxigenic *E. coli*. The Y_1 adrenal cell assay(8) and suckling mouse assay were used for enterotoxin testing. Rotavirus antigen in the stool was detected using an ELISA assay(10).

Clinical and laboratory follow-up was maintained throughout the patinet's hospitalization at regular intervals. Patients were discharged 24 hours after diarrhea stopped.

Table 2 shows the characteristics of the adult patients receiving either sucrose or glucose solution. The groups were comparable. About half of the adults had bacteriologically confirmed cholera.

Table 3. Success Rates of Adult Cholera-like Patients

	Sucrose Group		Glucose Group	
Overall success rate	56/75	(75%)	61/73	(84%)
Success in patients with 10% dehydration	38/51	(75%)	36/45	(80%)
Success in patients with 7.5% dehydration	18/24	(75%)	25/28	(89%)
Success in patients with *V. cholerae*	22/36	(61%)	31/43	(72%)
Success in patients with Enterotox. *E. coli*	24/27	(89%)	24/24	(100%)

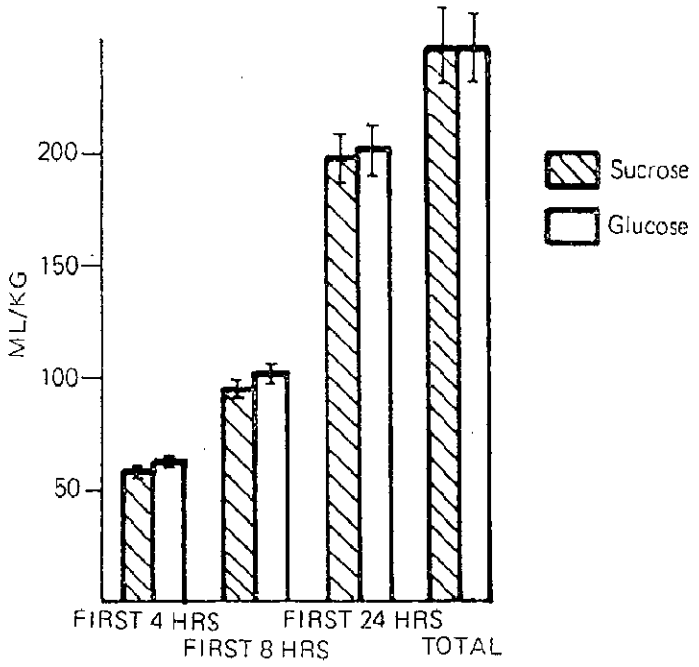

Figure 1. Oral Fluid Intake Rates in Adult Pateints with Cholera-like Diarrhea

Table 3 shows the success rates for the two groups of adult patients. The overall success rate was 75% for sucrose and 84% for glucose. This difference is not statistically significant. The success rates for those patients with 5% dehydration and with 7.5% dehydration are not significantly different. The success rate for patients with *E. coli* infections was, however, significantly better than for cholera patients for both sucrose and glucose groups ($p<0.05$).

Figure 1 shows that the mean (± S.E.) oral fluid intake rates were similar for the two groups during their illness. There did not seem to be any tendency for patients receiving sucrose to drink excess quantities of solution. Likewise the purging and vomiting rates were similar for the two groups as shown on Figure 2. Most of the purging in both groups occurred in the first 24 hours.

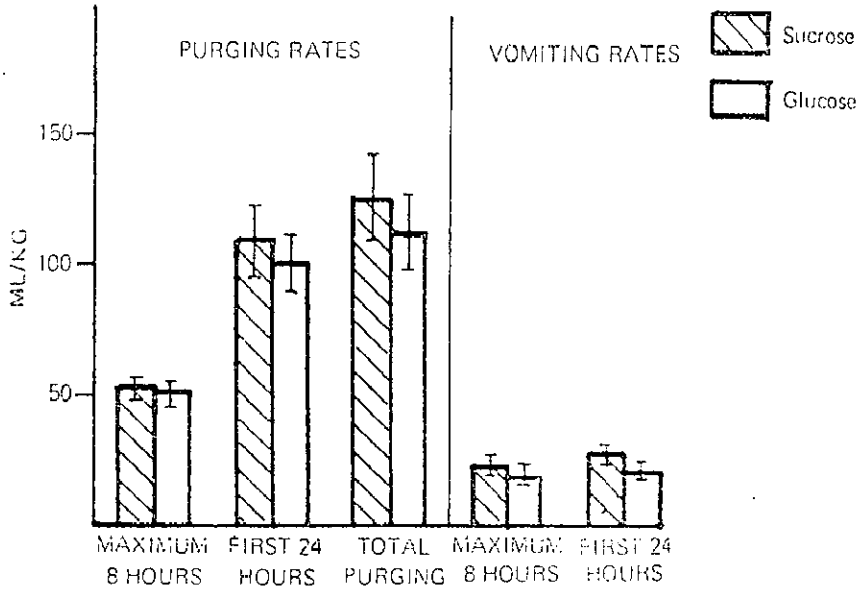

Figure 2 Fluid Losses in Adjults with Cholera-like Diarrhea Receiving Either Sucrose or Glucose Oral Solution

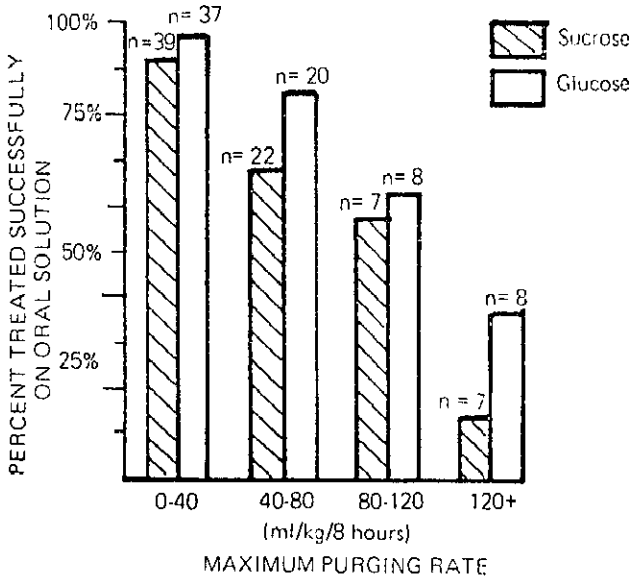

Figure 3. Association of Purging Rate with Oral Solution Success in Adults with Cholera-like Diarrhea

Figure 3 shows that the primary determinant of success of oral therapy was the purging rate in that the success rate decreased with increasing purging rate. While none of the differences between sucrose and glucose are significant, all groups show a better success rate for glucose.

The results of the children's cholera study are similar to the adult study. Table 4 shows that the children's groups were also comparable.

Table 4. Admission Characteristics of Child Cholera-like Patients

	Sucrose Group	Glucose Group
Number	55	56
Age (mths)	38±2*	40±1
Sex (M.F)	32:22	35:21
Duration of diarrhea prior to admission (hrs)	13± 2	11± 1
No. with 10% dehydration	41 (75%)	48 (86%)
Mean serum specific gravity	1.034	1.032
Mean serum bicarbonate (meq/l)	12.7±0.5	12.9±0.4
Enteric pathogens isolated:		
V. cholerae	53 (96%)	49 (88%)
Enterotox. *E. coli* (without *V. cholerae*)	1 (2%)	3 (5%)
No pathogen	1 (2%)	4 (7%)

* Mean ± Standard Error.

In contrast to the adults nearly all of these patients had bacteriologically confirmed cholera and were in general more severely dehydrated. The success rates for children, shown in Table 5, are somewhat lower than for the adults though again the differences between the sucrose and glucose groups are not significant. For children with cholera, the success rates were nearly identical.

Table 5. Success Rates of Child Cholera-like Patients

	Sucrose Group	Glucose Group
Overall success rate	40/55 (73%)	43/56 (77%)
Success rate in patients with 10% dehydration	28/41 (68%)	35/48 (73%)
Success rate in patients with 7.5% dehydration	12/14 (86%)	8/ 8 (100%)
Success rate in patients with *V. cholerae*	39/53 (74%)	36/49 (73%)

Figure 4 shows that the intake rates were the same for the two groups and Figure 5 shows that the purging and vomiting rates are also the same in the two groups.

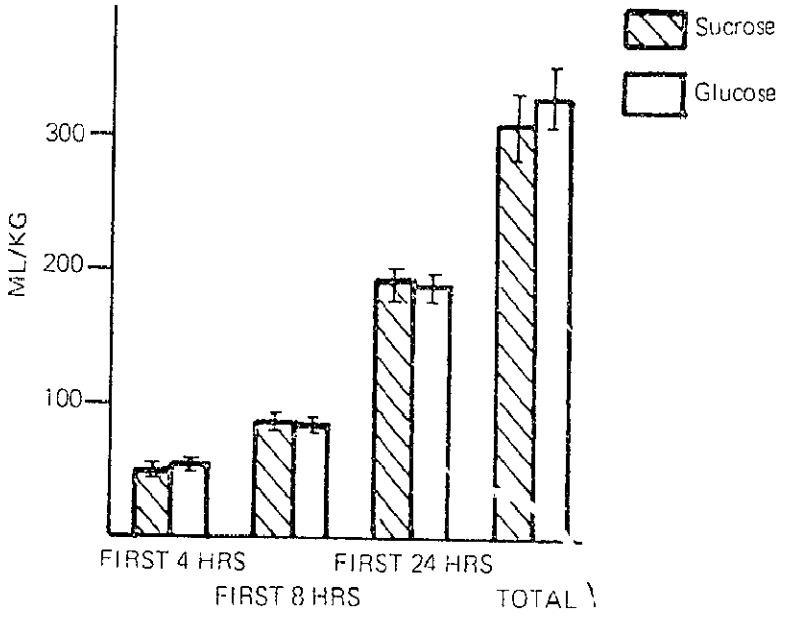

Figure 4. Oral Fluid Intake Rates in Children with Cholera-like Diarrhea Receiving Either Sucrose or Glucose Oral Solution

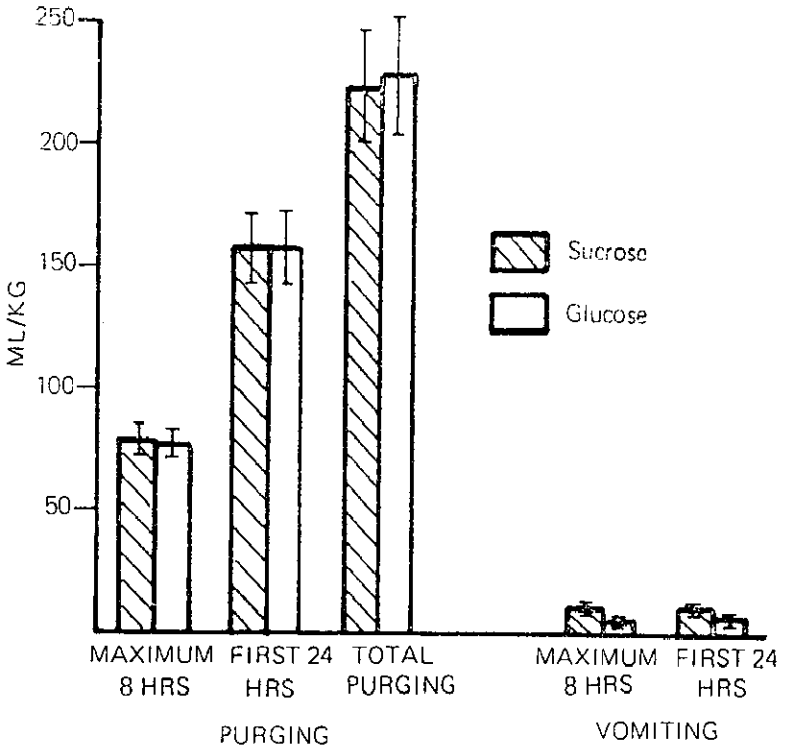

Figure 5. Fluid Losses in Children with Cholera-like Diarrhea Receiving Either Sucrose or Glocose Oral Solution

Figure 6 shows that failures were generally found in patients with heavy purging. As with the adults, the differences between the sucrose and glucose groups are not significant though the trend suggests a slight advantage for glucose, especially in patients with higher purging rates.

The groups of patients included in the sutdy of rotavirus diarrhea is shown on Table 6. The double blind rotavirus study included 89 children; 57 of these had rotavirus antigen in their stool. Because of the specific questions concerning oral therapy in rotavirous diarrhea, these 57 patients were analyzed

Table 6. Admission Characteristics of Children with Rotavirus Diarrhea

	Sucrose	Glucose	I.V.
Number	28	29	44
Age (mths)	11±1*	12±1	13±1
Duration of diarrhea prior to adm (hrs)	57±5	50±5	48±4
History of vomiting	27/28	29/29	42/44
Serum specific gravity	1.027±0.001	1.027±0.001	1.027±0.001
Serum bicarbonate	14.2±0.6	14.0±0.4	14.2±0.6
Stool sodium	23±3	17±4	32±3

* Mean ± Standard Error.

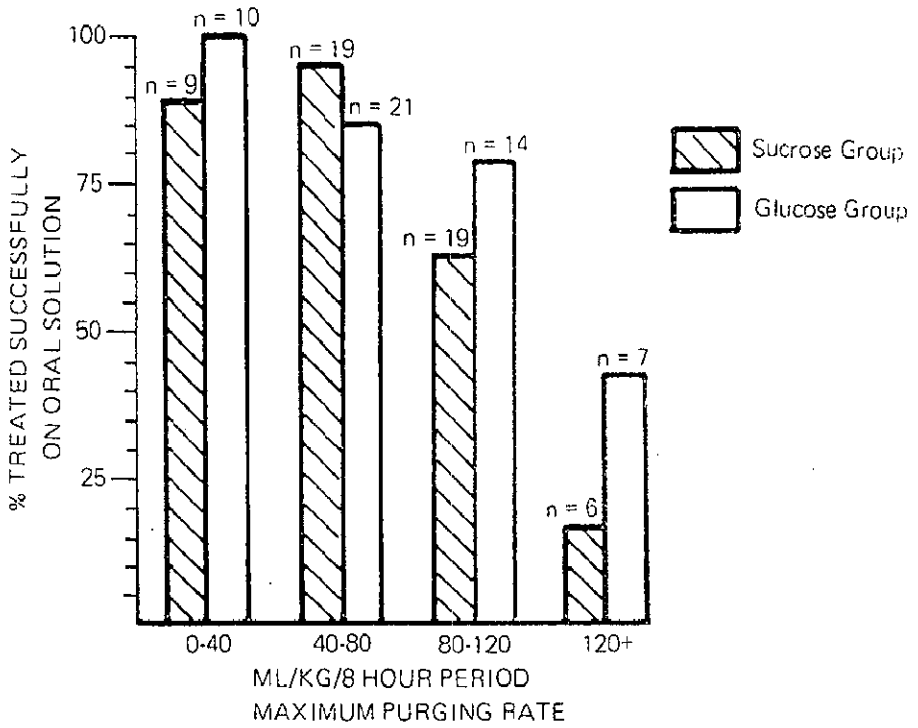

Figure 6. Association of Purging Rate with Oral Solution Success Rate in Children with Chlera-like Diarrhea

separately. These children were younger and less severely dehydrated than the cholera patients. In addition to the patients in the oral therapy groups, this table also shows a comparison with a group of rotavirus patients treated only with intravenous fluid. The I.V. comparison group consisted of children admitted to another study and were not part of the controlled trial, but were comparable.

All patients with rotavirus succeeded.

Figure 7 shows the purging rates in the three groups. The purging rates for the sucrose group were somewhat higher, especially during the second 24 hours, but again these differences were not significant. The intravenously treated group purged similar quantities as the sucrose group. The intake rates and the rate of rehydration, as measured by weight gain, time until first urination, and change in serum specific gravity were not different between the two oral solution groups.

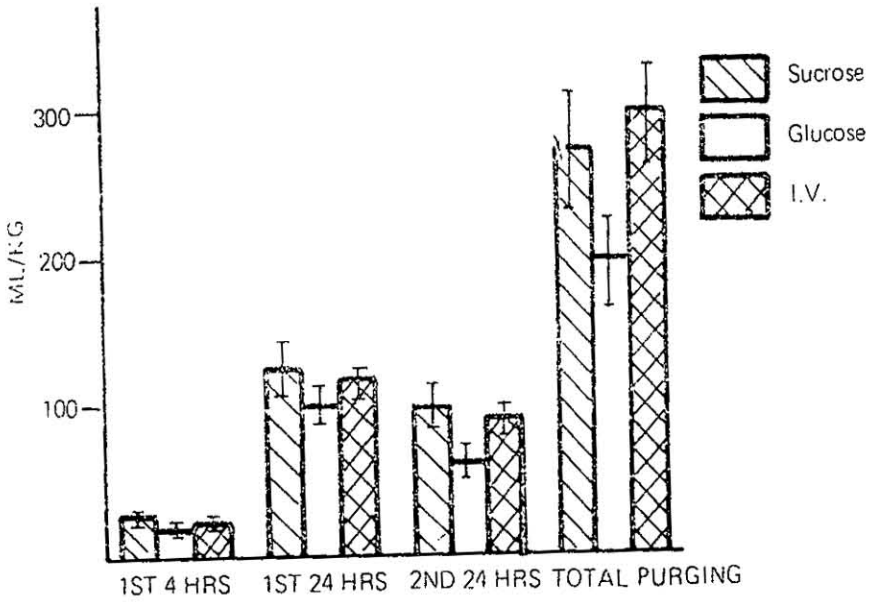

Figure 7. Purging Rates in Rotavirus Patients Receiving Oral Therapy or Intravenous Therapy

The mean (± Standard Error) stool reducing substance concentration for the rotavirus groups is shown on Figure 8. Unlike patients with enterotoxigenic diarrhea, patients with rotavirus had large amounts of reducing substance in their stool demonstrated after hydrolysis, but this was found in both oral therapy groups suggesting a defect in carbohydrate digestion in rotavirus infection related to food intake rather than a specific sucrase deficiency. Further work on the nature of the carbohydrate maldigestion is planned. The use of the finding that sucrose solution is effective, especially in patients with lower purging rates, a sucrose based solution is now being used in the oral rehydration centers at Dacca and Matlab. At the time of its introduction at Matlab, the change was not announced to the staff. At the time of the switch, rotavirus surveillance was ongoing. Subsequently, a retrospective analysis of the success of the oral therapy solutions was made in patients with confirmed rotavirus diarrhea. In this analysis, "failure" was defined again as the need for unscheduled intravenous therapy; however, the determination of the need for intravenous therapy was made by the atten-

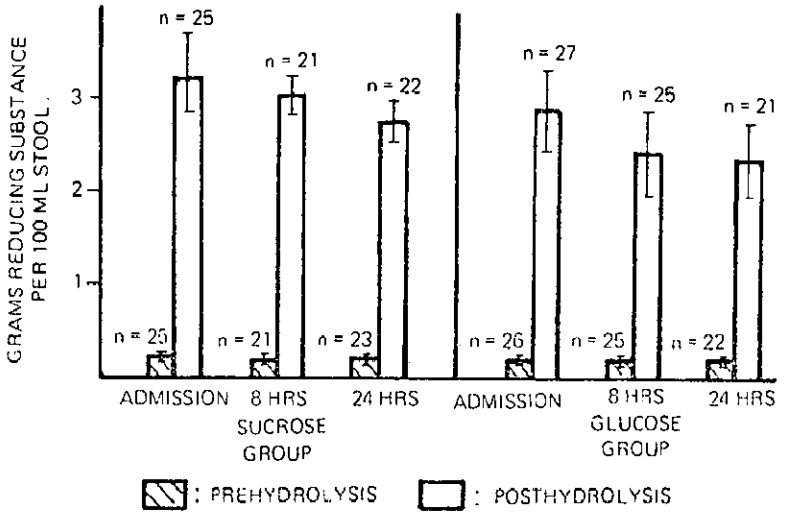

Figure 8. Stool Reducing Substances Before and After Hydrolysis in Rotavirus Patients Receiving Sucrose or Glucose Oral Solution

dant who was not aware of the study.

The success rates for the two oral solutions is shown on Table 7. The success rates were 88.5% and 93.5% for the two groups in patients with no or mild dehydration initially and 84.3% and 88.1% for patients with moderate to severe dehydration who were initially rehydrated intravenously before being switched to oral maintenance therapy. In addition to these patients who continued to purge while at the treatment center, an additional 296 patients with no dehydration, but with rotavirus antigen and a history of diarrhea, were discharged after a four hour observation period. The differences between the sucrose and glucose groups again show a trend in favor of glucose, but even with these large numbers, are not significant.

Table 7: Success Rates of Children with Rotovirus Diarrhea at Matlab

	Sucrose	Glucose
Documented Purging Patients:		
Patients with no or mild dehydration	178/201 (88.5%)	202/216 (93.5%)
Patients with moderate to severe dehydration initially given intravenous fluid	27/32 (84.3%)	37/42 (88.1%)
Total	205/233 (88.0%)	239/258 (92.6%)
History of Diarrhea but No Observed Purging During 4 Hours of Observation	170	126

Complications of oral therapy should be mentioned. The most serious complication we observed was vomiting and aspiration. This occurred in two patients; one of whom, a child with cholera, died. The complication in this patient developed secondary to hypoglycemia and a convulsion with subsequent vomiting and aspiration.

Secondly, sugar intolerance may occur occasionally. We observed sucrose intolerance in one child and one adult both of whom had diarrhea of unknown etiology. The sucrose intolerance was responsible for oral fluid failure in the child but not the adult. We did not observe glucose intolerance.

Third, hypoglycemia may be a complication of cholera in children. The sugar in the oral solution may not necessarily be sufficient to prevent this as demonstrated in the fatal case.

Finally vomiting was very common in the cholera patients, especially in those patients who were rehydrated with oral therapy. While we learned that rehydration is possible in most patients not in shock with moderate to severe dehydration, it requires persistence. Whenever available, complete intravenous rehydration is preferable for patients with this degree of dehydration.

In summary, sucrose and glucose oral solutions have been compared in four clinical settings in Bangladesh. These studies which show a trend toward a higher success rate for glucose are consistent with other studies by Palmer *et al.* (4) and Nalin *et al.* (11). The combined results of all these studies taken together suggest that this trend is real but small. The difference, however, apparently increases with increasing purging rates. For mild non-cholera diarrhea both solutions are nearly always effective. The slight advantage for glucose would suggest that glucose should continue to be used in such prepackaged materials as "Oralyte." Local and national health planners will have to decide which sugar to use depending on a local assessment of availability, cost and distribution of ingredients. They can be assured, however, that sucrose is an effective alternative to glucose.

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