CLINICAL TRIAL

Effects of food with two oral rehydration therapies: a randomised controlled clinical trial

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Abstract

To evaluate the impact of food on the efficacy of oral rehydration solution (ORS), a randomised, controlled clinical trial was conducted in 182 adults with cholera. After initial rehydration with an intravenous polyelectrolyte solution for four hours, the patients were randomised to receive one of four rehydration therapies: glucose based ORS and no food for the first 24 hours (group A), glucose based ORS plus food from the beginning of treatment (group B), rice based ORS with no food for the first 24 hours (group C), and rice based ORS plus food from start of therapy (group D). Tetracycline was given after 72 hours to all patients. No significant differences in ORS intake, stool output, and duration of diarrhoea were noted between groups A and B and between groups C and D. A substantial and significant reduction in stool output was, however, shown in the groups who received rice based ORS irrespective of feeding. These results show that food does not potentiate the efficacy of either glucose based or rice based ORS in adults with cholera. Rice based ORS compared with glucose ORS substantially reduces purging in cholera patients.

Rehydration therapy with the present glucose based oral rehydration solution recommended by the World Health Organisation (WHO-ORS) does not reduce the volume or frequency of stools.¹⁻⁴ Since many water soluble organic molecules, including glucose, can enhance the absorption of sodium from the small intestine,⁵ it has been suggested that optimum exploitation of this phenomenon could lead to the development of an improved ORS formulation that would not only successfully replace the deficit of salts and water in diarrhoea but also actively induce absorption, with reduction of the stool volume and duration of diarrhoea.⁶ Based on this suggestion, cereal based ORS formulations have been shown to reduce stool volume, vomiting, and ORS consumption.⁷⁻⁹ Rice powder is the usual constituent of these mixtures and contains complex carbohydrate and protein which, on digestion, should slowly liberate glucose, oligosaccharides, small peptides, and amino acids and accelerate salt and water absorption without any osmotic penalty. Starches and proteins in mixed

diets (cereal, lentil, meat, and fish) release glucose, amino acids, and short chain peptides, all of which enhance absorption of sodium and water. Similarly, mixed food might be expected to convert a complete glucose electrolyte solution into an improved ORS.

In this study, we have examined the effect of giving a large conventional meal (usually eaten by Bangladeshi people) with ORS. In addition, we have compared rice containing ORS with glucose based ORS to determine which is better in the treatment of cholera patients.

Patients and methods

This study was carried out between July 1986 and December 1988. Adults (15 to 60 years) of either sex with a history of watery diarrhoea for 24 hours or less and with moderate or severe dehydration, presence of *Vibrio cholerae* in fresh stool specimen by dark field microscopic examination, and no history of antidiarrhoeal or antimicrobial drug consumption before admission were included in the study. Written informed consent was obtained from the patients or their legal guardians. The study was approved by the Ethical Review Committee of this institution.

At admission to hospital the body weight of each patient was determined and a thorough clinical examination was undertaken by one of the investigators. The dehydration status of the patients was assessed according to WHO guidelines.¹⁰ Patients with moderate dehydration had increased thirst, sunken eyes, lost skin turgor, and low volume peripheral pulses (estimated loss of body weight (6-9%). Patients with severe dehydration had additional features of hypovolaemic shock such as cold, sweaty hands and feet, and very feeble or imperceptible peripheral pulses (estimated loss of body weight $\geq 10\%$). All patients were given intravenous polyelectrolyte solution containing Na^+ , 133 mmol/l; Cl^- , 98 mmol/l; K^+ , 13 mmol/l; and the equivalent of bicarbonate (in the form of acetate) 48 mmol/l for four hours to correct dehydration completely. The patients were then assigned to one of the following treatment regimens according to random numbers:

Group A - WHO-ORS. Food was withheld for the first 24 hours but was then offered. (The food offered to all groups was similar - boiled rice, bread, fish, chicken, egg, milk, and lentil);

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TABLE I Clinical characteristics and baseline information at admission of the four different treatment groups (values are mean (SD) or number)

	Group A WHO-ORS without food for 24 h (n=47)	Group B WHO-ORS and food from start of treatment (n=42)	Group C Rice ORS without food for 24 h (n=46)	Group D Rice ORS and food from start of treatment (n=47)
Age (yrs)	26.3 (8.5)	28.3 (9.1)	28.7 (9.9)	30.2 (10.6)
Sex (M/F)	24/23	26/16	22/24	31/16
Admission body weight (kg)	39.4 (5.6)	39.7 (5.1)	38.6 (5.9)	40.0 (4.9)
Body weight after 4 h (baseline) iv rehydration	44.0 (6.2)	44.5 (5.0)	43.3 (5.9)	44.9 (5.5)
Duration of diarrhoea before admission (h)	10.4 (4.9)	11.1 (5.5)	10.9 (5.2)	11.8 (6.4)
No with severe/moderate dehydration on admission	47/0	42/0	45/1	46/1
Baseline stool volume (ml/kg/4 h)	36.6 (32.6)	44.2 (37.5)	36.5 (28.8)	35.2 (28.8)
Baseline iv fluid (ml/kg/4 h)	164.4 (39.5)	174.9 (43.7)	170.9 (36.3)	162.5 (36.7)
Types of <i>Vibrio cholerae</i> isolated:				
Classical	18	20	21	25
Eltor	29	22	25	22

Group B – WHO-ORS and food (as above) from the beginning of ORS therapy;

Group C – rice based ORS and no food for the first 24 hours;

Group D – rice based ORS and food from the beginning of ORS therapy.

The patients drank ORS freely and were also allowed plain water. Patients were given three meals daily: breakfast (bread, milk, egg, and sugar) at 7.00 am, lunch (boiled rice, fish/meat, lentil) at 12.00 noon, and supper (food as in lunch) at 7.00 pm, following the usual custom. All items of food were weighed before serving and the weight of left over food was subtracted from that offered to determine the amount the patient had consumed. The caloric value was calculated from the known values of the offered food estimated by adiabatic bomb calorimeter. Careful records of intake of ORS and plain water and the output of stool, urine, and vomit were kept and summarised at eight hourly intervals until the diarrhoea stopped. The end of diarrhoea was indicated by the passage of the first soft stool and/or no stool for 16 hours. Body weight was determined at admission, four hours after initial rehydration, and then every eight

hours until the patient was discharged. The duration of diarrhoea was defined as the duration in hours from the time of admission to the passage of the last loose or watery stool. If a patient failed to maintain hydration with ORS because of extreme purging and excessive vomiting and developed moderate or severe dehydration at any time between the beginning of the study and the end of diarrhoea, intravenous fluid was given rapidly to correct dehydration and then the patient was given the assigned ORS. These events are referred to as unscheduled intravenous fluid therapy. Data from these patients were also included in the analysis. Tetracycline was given orally after 72 hours to all patients at a dose of 500 mg six hourly for two days.

Stool specimens for culture of *Vibrio cholerae*, *Salmonellae*, and *Shigellae* and for microscopic examination to identify intestinal parasites were taken on hospital admission. Haematocrit, serum specific gravity, and serum concentrations of sodium, potassium, chloride, and bicarbonate on admission, at four hours, and at 24 hours after initial rehydration were measured.

Clinical characteristics such as age, sex, and body weight on admission, duration of diarrhoea before admission, amount of intravenous fluid given, and baseline purging rates were compared between the groups. Major outcome variables such as stool output (ml/kg), intake of ORS (ml/kg), and duration of diarrhoea (hours) were compared between the groups (group A v group B, group C v group D, group A v group C, and group B v group D) using Student's *t* test. The χ^2 test was used for dichotomous variables – for example the number of patients who received unscheduled intravenous fluid and number of patients who vomited during the study period. Factorial analysis was also carried out using analysis of variance to evaluate ORS type and feeding status during first 24 hours and interaction between them on first 24 hours' stool output. Data were analysed in microcomputer using data analysis package (SPSS/PC+ Inc, USA).

TABLE II Comparison of clinical outcome in the four different treatment groups (values are mean (SD) or number)

	Group A WHO-ORS without food for 24 h (n=47)	Group B WHO-ORS and food from start of treatment (n=42)	Group C Rice ORS without food for 24 h (n=46)	Group D Rice ORS and food from start of treatment (n=47)
Fluid intake (ml/kg over 0–24 h):				
ORS	518 (196)*	452 (193)*	338 (122)*	305 (108)*
Water	19 (21)†	36 (40)†	42 (29)	52 (30)
Output (ml/kg over 0–24 h):				
Stool	391 (157)*	366 (174)*	227 (119)*	223 (128)*
Urine	137 (74)†	101 (61)†	96 (70)	106 (57)
Total fluid intake (ml/kg):				
ORS	993 (447)*	828 (446)*	565 (265)*	526 (253)*
Water	104 (53)	136 (90)	153 (94)	165 (83)
Total output (ml/kg):				
Stool	742 (388)*	712 (357)*	440 (294)*	476 (359)*
Urine	355 (165)	304 (177)	247 (160)	284 (139)
Calorie intake (kcal, 0–24 h)	—	1067 (498)	—	1034 (522)
Duration of diarrhoea (h)	86.3 (22.2)	85.2 (19.9)	77.8 (26.3)	81.1 (23.8)
No of patients with unscheduled iv fluid in 1st 24 h	8	15	6	9
No of patients with unscheduled iv fluid during treatment	18	20	18	20
No of patients vomited during treatment	28	27	28	29

* (Group A v group C; Group B v group D $p0<.05$).
† (Group A v group B $p0<.05$).

increased significantly in the first 24 hours compared with group B (WHO-ORS and fed from the start of therapy) where water intake was increased and urine output reduced.

Factorial analysis further confirmed that food had no effect in reducing stool volume during initial 24 hours ($F=0.43$, $p=0.51$) and the effect of rice ORS in reducing stool volume was highly significant ($F=51.0$, $p<0.001$). This analysis also showed that there was no interaction between ORS type and feeding status during first 24 hours ($F=0.22$, $p=0.64$).

Duration of diarrhoea was similar in all groups. Calorie intake from food during the first 24 hours in group B and group D was not statically different. The number of patients who received unscheduled intravenous fluid and the number of patients who vomited during the study period in all groups were also not significantly different. On admission, at four hours, and at 24 hours after ORS therapy the values of serum specific gravity, haematocrit, sodium, potassium, chloride, and total carbon dioxide were comparable in all treatment groups.

Discussion

In recent years, continued feeding during diarrhoea, in addition to oral rehydration therapy, has become well accepted as preventing malnutrition. However, very few studies have evaluated the role of giving food with ORS on clinical outcome during the treatment of acute diarrhoea. We hypothesised that eating a normal diet along with ORS may provide more substrates and help in better absorption of salt and water from the intestine and influence the clinical recovery of patients.

Our study shows that ORS plus food during the early part of the illness had no added advantage in reducing stool volume, vomiting, and duration of diarrhoea. Why food failed to produce any positive impact on the efficacy of ORS cannot be explained by this study. It may be assumed that glucose based ORS associated with food might have caused osmotic diarrhoea. Secondly, rice based ORS could have exerted the maximum effect on salt and water absorption leaving no room for an added effect of food. Similar findings were demonstrated in an earlier study in which WHO-ORS plus boiled rice in the early part of diarrhoeal illness was no better than WHO-ORS alone in the treatment of children with cholera.¹¹ A previous study has reported a significant reduction in stool volume in cholera patients treated with rice based compared with glucose based ORS during the first 24 hour period when food was withheld. But the difference disappeared when food was introduced after 24 hours.¹² It raises a question whether the early introduction of food could have shown the same beneficial effect. However, another study has shown that the addition of food to glucose based ORS was associated with an approximately 42% reduction in stool volume and the duration of diarrhoea.¹³ In this study, infants in the starved group drank substantially more glucose ORS in place of food and this could have contributed to osmotic diarrhoea. Also, the subjects were infants suffering from non-cholera

diarrhoea, whereas in our study the subjects were adult cholera patients. It is expected that cholera patients suffer from severe diarrhoea with a high purging rate compared with non-cholera patients. The severity of the illness in our patients was also reflected by the failure of more patients to maintain hydration with ORS and the prolonged duration of diarrhoea compared with patients in previous reports.^{14,15} Moreover, an antibiotic was given after 72 hours in our study, whereas it was used within or after 24 hours in the studies referred to above.

The reduction in stool seen in both groups of patients receiving rice based ORS with or without food in our study agrees with the previous reports.⁷⁻⁹ In addition, our results suggest that food did not potentiate the efficacy of either glucose or rice based ORS in the treatment of adult cholera patients.

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