Comparison of Three Oral Rehydration Strategies in the Treatment of Acute Diarrhea in a Tropical Country

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ABSTRACT

Background: The administration of hydrating solutions and early refeeding improve recovery for infants and children with diarrhea.

Objective: The aim of this study was to assess the efficacy of a low-osmolarity (30 mEq/L Na⁺) solution administered after the standard, high-osmolarity (90 mEq/L Na⁺) solution via a nasogastric tube (NGT) and followed by early refeeding to achieve more rapid body weight recovery in infants and children with acute diarrhea.

Methods: Infants and children aged <5 years with acute diarrhea and dehydration (body weight loss of ≥10%) observed from January to August 2001 at Saint Camille Medical Center, Ouagadougou, Burkina Faso, were enrolled. Patients were randomized to 1 of 3 treatment protocols. Patients in group A received, via NGT, rehydration with a high-osmolarity solution for 3 hours, followed by a low-osmolarity solution for at least 3 additional hours. Patients in group B were given only a low-osmolarity solution via NGT. In group C, rehydration was carried out using a high-osmolarity solution via NGT.

Results: Four thousand consecutively treated infants and children (2010 boys, 1990 girls; mean [SD] age, 3.5 [2.7] years) were enrolled. After the first 6 hours of infusion, 90% of the patients who had received the combined rehydration (group A) showed significant body weight recovery, versus 80% and 79% of the patients in groups B and C, respectively. Stool output significantly decreased for group A compared with groups B and C (114 vs 125 and 120 g/kg, respectively). Only 7% of the patients in group A required prolonged rehydration (>6 hours) with the low-osmolarity solution, versus 10% and 12% in groups B and C, respectively. A total of 3% of patients treated with combined rehydration required hospitalization, compared with 10% and 9% in groups B and C, respectively. At the end of infusion, 25% of the patients rehydrated only with a low-osmolarity solution showed poor body weight recovery and appeared lethargic,

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versus 10% in group A and 15% in group C. Patients who were rehydrated with a high-osmolarity solution showed symptoms of hypernatremia (serum Na^+ concentration >140 mEq/L). At the end of rehydration (≥ 6 hours), all patients recovered their previous body weight, partially or totally, and refeeding was begun. Rehydration and diet were continued at home, or in neighboring areas for those living far away.

Conclusions: In this study population, the administration of a high-osmolarity solution followed by a low-osmolarity solution and early refeeding was effective in the treatment of acute diarrhea and was well tolerated. (*Curr Ther Res Clin Exp.* 2003;64:189–202) Copyright © 2003 Excerpta Medica, Inc.

Key words: low-osmolarity rehydration, refeeding, diarrhea.

INTRODUCTION

Diarrheal diseases represent a major public health problem worldwide. In developing countries, it is estimated that >2 million people, mostly infants and children, die of dehydration due to diarrhea each year. Diarrhea remains a common problem in developed countries; in the United States, 7% of children with acute diarrhea require hospitalization each year.¹

Acute diarrhea can be treated orally or via nasogastric tube (NGT), depending on the degree of dehydration. Antibiotic therapy should be administered to patients whose diarrhea is associated with infection with *Vibrio cholera*, *Shigella* spp., or *Escherichia coli*, and antiparasitic drugs should be given for *Entamoeba* spp., *Trichomonas* spp., and *Giardia lamblia* infections.

Morbidity and mortality associated with diarrheal diseases are reduced with the administration of an oral rehydration solution (ORS).² The World Health Organization (WHO)³ has recommended a high-osmolarity (90 mEq/L Na^+) mixture of glucose and 3 salts (20 g glucose, 3.5 g sodium chloride [NaCl], 2.5 g sodium bicarbonate [NaHCO_3], and 1.5 g potassium chloride [KCl], in 1 L water). This treatment has been proved to be safe and effective in treating and preventing dehydration, especially in developing countries.³ ORS given via NGT, followed by early refeeding, can be used to avoid the difficulties of venous infusion of glucose and electrolytes in the hospital setting.⁴ However, solutions with high Na^+ content can be inconvenient due to reduced tolerance to Na^+ load in children (resulting in an increased risk for hypernatremia) and an osmotically driven increase in stool output. Solutions with lower osmolarity^{5–7} have been tested in industrialized and developing countries (where infection with *V. cholera* is endemic⁸) by replacing glucose with a complex carbohydrate or reducing the concentration of glucose and salts in the solution.

The aim of this study was to assess the efficacy of a low-osmolarity (30 mEq/L Na^+) solution administered after the standard, high-osmolarity (90 mEq/L Na^+) solution via NGT and followed by early refeeding to achieve more rapid body weight recovery in infants and children with acute diarrhea.

PATIENTS AND METHODS

This study was conducted from January to August 2001 at the Saint Camille Medical Center (SCMC, Ouagadougou, Burkina Faso), with the cooperation of the Sisters of Saint Camille working in the Pediatric Section of the SCMC. Twenty or more infants and children with acute diarrhea are admitted to this facility daily. The study protocol was approved by the SCMC ethics committee.

Patients

Infants and children aged <5 years with acute diarrhea and dehydration (body weight loss $\geq 10\%$) were enrolled using the Consolidated Standards of Reporting Trials (CONSORT) criteria.⁹ Severity of dehydration was assessed according to WHO guidelines³ (Table I); body weight loss was determined using a comparison of baseline body weight with that recorded in the patient's medical chart at his or her last clinic visit. Duration of diarrhea and the distance between the village of origin and SCMC also were considered in assessing the severity of dehydration. The exclusion criterion was dehydration with shock, which requires rapid transfer to a hospital for intensive care.

It was suggested to the parents of all study patients that they choose the proposed treatment. All parents provided written consent for participation.

Methods

Patients were randomized to 1 of 3 rehydration protocols. Group A was given a high-osmolarity (90 mEq/L Na^+) solution (20 g glucose, 3.5 g NaCl, 2.5 g NaHCO_3 , and 1.5 g KCl, in 1 L water), administered by NGT over 3 hours, followed by a low-osmolarity (30 mEq/L Na^+) solution given by NGT for 3 additional

Table I. World Health Organization guidelines³ for the assessment of dehydration* in children with diarrhea.

Test	No Dehydration	Mild to Moderate Dehydration	Severe Dehydration
General appearance	Well, alert	<i>Restless, irritable</i>	<i>Lethargic or unconscious; floppy</i>
Eyes	Normal	Sunken	Very sunken, dry
Tears	Present	Absent	Absent
Mouth and tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	<i>Thirsty, drinks eagerly</i>	<i>Drinks poorly or not able to drink</i>
Skin pinch	Goes back quickly	<i>Goes back slowly</i>	<i>Goes back very slowly</i>

*Defined as patient having 2 or more of these signs, including at least 1 sign appearing in italics.

hours. Group B received only a low-osmolarity solution (20 g glucose, 1.2 g NaCl, 0.8 g NaHCO₃, and 1.5 g KCl, in 1 L water), administered by NGT over 6 hours. Group C was given a high-osmolarity solution only, containing glucose and electrolytes according to the WHO guidelines,³ administered by NGT over 6 hours. For every 10 consecutive children randomized to group A, only 1 child was randomized to group B or C. Rehydration was started a few minutes after randomization. The investigators were not blinded to treatment assignment.

For all 3 treatment protocols, ~30 mL/kg of ORS was administered as rapidly as possible (in 30 minutes), followed by 70 mL/kg over the next 6 hours. The approximate amount of ORS given over 6 hours is reported in Table II.

Patients were to undergo stool and blood sample collection before and 6 to 7 hours after the start of rehydration with the collaboration of a nurse. The assessments for efficacy and tolerability were done in accordance with the WHO guidelines³ (Table I). Stool samples were assessed by laboratory staff at SCMC, using microscopic examination to identify the presence of parasites (eg, vegetative forms, protozoan cysts, helminthic eggs), or leukocytes. Blood samples were analyzed by the same laboratory to determine serum electrolyte (Na⁺ and K⁺) and calcium concentrations in patients whose parents provided consent.

At the end of 6 to 7 hours, if signs of severe dehydration persisted, rehydration was continued. If signs of mild to moderate dehydration persisted, the procedures for rehydration were repeated and refeeding and other fluids started. If no signs of dehydration were found, rehydration was maintained using ongoing fluid-loss replacement and refeeding was started.

No sedative or antiemetic drugs were given, except in the case of irrepressible vomiting; in this situation, the infusion was given in a room (Figure) near the ambulatory care center, with the continuous assistance of a parent. At the end of the therapy, the patients were given a mixture of millet (60%), soybeans (20%), peanut paste (10%), sugar (9.0% to 9.5%), and salt (0.5% to 1.0%), according to the formula suggested by the Burkina Faso Association of Misola, at 20% to 25%.

A 7-day course of antibiotic or antiparasitic therapy was started after the patient was well rehydrated (usually in 6 to 7 hours) and vomiting had stopped. Metronidazole (35 to 50 mg/kg daily, divided into 3 doses and given orally) was prescribed if protozoa (eg, *G lamblia*, *Trichomonas* spp., *Entamoeba* spp.) or

Table II. Baseline characteristics determining amount of oral rehydration solution administered via nasogastric tube over the first 6 hours of treatment.

Baseline Characteristic	Total Amount, mL			
	200 to 400	401 to 600	601 to 800	801 to 1200
Age	<4 mo	4 to 11 mo	12 to 23 mo	2 to 4 y
Body weight, kg	<5	5 to <8	8 to <11	11 to <16

Figure. (A) The room where rehydration via nasogastric tube was carried out (20 or more children a day with the assistance of 1 nurse). (B) Nasogastric hydration (the tube locked into the nostril is connected to a bottle containing the rehydration solution).

protozoan cysts were detected in the stool. Trimethoprim (5 mg/kg daily) plus sulfamethoxazole (25 mg/kg daily, divided into 2 doses and given orally) were prescribed if leukocytes were detected in the stool.

Also, at the end of rehydration therapy (≥ 6 hours), refeeding was initiated using either breast-feeding (in infants whose mothers were present) or with Misola.

After the assessment on the same day, parents were instructed to return to the SCMC if any of the following signs developed: an increase in the frequency of watery stools, eating or drinking poorly, marked thirst, repeated vomiting, fever, or bloody stool. Patients with no signs of dehydration were sent home with packets containing enough ORS for 2 days. Each parent was shown how to prepare and administer the solution.

Efficacy and Tolerability Analyses

Because urine output decreases as dehydration develops and resumes within 6 to 8 hours after rehydration is started, regular urination (every 3 to 4 hours) is a sign that enough fluid is being given. The quantity and frequency of urination also was assessed by a nurse for each patient.

The 4 outcome variables used to assess the impact of these 3 treatment protocols were as follows: (1) the mean stool output (g/kg) in the 24 hours after rehydration was started; (2) the proportion of patients who required supplementary IV therapy at the hospital; (3) the number of patients who vomited in the first 24 hours; and (4) the mean duration of diarrhea after rehydration was started and significant body weight was recovered (ie, $\geq 10\%$ body weight gain from baseline).

Statistical Analysis

Analysis of variance or Student *t* test was used to assess the response to the different protocols using the Statistical Package for Social Sciences version 10 (SPSS Inc., Chicago, Illinois). Statistical significance was set at $P \leq 0.05$.

RESULTS

Four thousand consecutively treated infants and children (2010 boys, 1990 girls; mean [SD] age, 3.5 [2.7] years) were enrolled. All children were of Mossi race and were dehydrated due to acute diarrhea. Only ~10% of patients in each group had severe dehydration, and this was considered during rehydration. The severity of dehydration in many of these children was the result of having to travel a long distance to reach the clinic. Some children needed more rehydration than others, and many had to be hospitalized.

Group A comprised 3400 patients; group B, 300 patients; and group C, 300 patients. The majority of patients were assigned to group A because it was better accepted by the patients and their parents, who appreciated the rapid improvement after rehydration.

Patients' clinical and laboratory data are summarized in Table III. Of the 3400 patients in group A, 90% had a rapid response to treatment compared with 80% and 79% in groups B and C, respectively ($P < 0.001$). As shown in Table IV, body weight recovery was significantly greater in group A (median, 8%; range, 7% to 10%) compared with groups B and C ($P < 0.001$ for both). However, after the rehydration period, no child's weight returned to the prediarrhea weight. Also, the mean stool output decreased significantly in group A compared with groups B and C (114 g/kg vs 125 and 120 g/kg, respectively; $P < 0.05$ for both) (Table IV).

Only 7% of patients in group A required prolonged rehydration (>6 hours) with the low-osmolarity solution, versus 10% and 12% in groups B and C, respectively ($P < 0.008$). Furthermore, only 3% of patients in group A required hospitalization (because of fatigue, frequent vomiting, or abdominal distension), compared with 10% and 9% in groups B and C, respectively (Table III). The mean serum electrolyte levels before and after rehydration were significantly lower in group B than in group A ($P < 0.001$). This difference was not significant versus group C (Table V).

In group B, 25% of patients recovered only a small amount of body weight and appeared lethargic compared with 10% of patients in group A and 15% in group C ($P < 0.001$). After rehydration, 90% of patients in group C showed symptoms of edema, and they were more lethargic than were the patients in groups A and B ($P < 0.001$ for edema symptoms and lethargy versus groups A and B). The serum levels of Na^+ and K^+ after treatment were significantly

Table III. Clinical and laboratory findings (no. [%] of study patients).

Finding	Group A (n = 3400)	Group B (n = 300)	Group C (n = 300)
Response to treatment			
Rapid response	3060 (90)	240 (80)	237 (79)
Need for prolonged rehydration	250 (7)	30 (10)	36 (12)
Need for hospitalization	90 (3)	30 (10)	27 (9)
Stool examination*			
Negative for pathogens	1651 (63)	145 (63)	147 (64)
Leukocytes	690 (26)	62 (27)	60 (26)
<i>Giardia lamblia</i> , <i>Trichomonas</i> spp., <i>Entamoeba</i> spp., <i>Shigella</i> spp., <i>Escherichia coli</i> , <i>Salmonella</i> spp.	271 (10)	25 (11)	23 (10)
Antibiotic therapy*			
TMP-SMX	690 (26)	62 (27)	60 (26)
Metronidazole	271 (10)	25 (11)	23 (10)

TMP-SMX = trimethoprim-sulfamethoxazole.

*n = 3074; 2612, 232, and 230 patients in groups A, B, and C, respectively.

Table IV. Response to rehydration therapy.

Patient Characteristic	Group A (n = 3400)		Group B (n = 300)		Group C (n = 300)	
	Baseline	Posttreatment	Baseline	Posttreatment	Baseline	Posttreatment
Mean body weight loss, %	>10	<2	>10	<5	>10	<3
No. of bowel movements/d*	8 (2)	2 (1) [†]	8 (2)	2 (1) [†]	8 (2)	2 (1) [†]
Duration of diarrhea, d*	2.0 (0.5)	0.5 (0.1) [†]	2.0 (0.5)	0.5 (0.1) [†]	2.0 (0.5)	0.5 (0.1) [†]
Lethargy	Moderately severe	Mild	Moderately severe	Moderate	Moderately severe	Moderate
Edema	—	—	—	—	—	Moderate

*Values are expressed as mean (SD).

[†]P < 0.001 versus baseline (analysis of variance).

Table V. Mean (SD) serum electrolyte (Na⁺ and K⁺) and calcium concentrations in study patients.

Electrolyte	Group A (n = 3400)		Group B (n = 300)		Group C (n = 300)	
	Baseline	Posttreatment	Baseline	Posttreatment	Baseline	Posttreatment
Na ⁺ , mEq/L	130 (2)	132 (2)	130 (2)	130 (2)*	130 (2)	135 (2)*
K ⁺ , mEq/L	3.7 (0.3)	4.5 (0.3)*	3.7 (0.3)	4.0 (0.3)*	3.7 (0.3)	3.9 (0.3)*
Calcium, mg/dL	8.8 (0.3)	9.2 (0.3)*	8.8 (0.3)	9.1 (0.3)*	8.8 (0.3)	9.2 (0.3)*

*P < 0.001 versus baseline (analysis of variance).

increased in group C compared with groups A and B ($P < 0.001$ for both), whereas the serum calcium level was similar in all groups (Table V).

No adverse events were observed in any patient as a result of rehydration via NGT. Pulmonary edema, which may occur when too large a volume of venous fluids is given in an attempt to correct metabolic acidosis, was not observed in our patients. Furthermore, renal failure did not occur when too little fluid was given, when shock due to hyponatremia and/or hypoglycemia was rapidly corrected, and when hydration was maintained according to the guidelines. No patients died as a result of adverse events.

A total of 3074 patients completed stool examination. The 1943 (63%) patients whose stool samples were negative for parasites (*G lamblia*, *Trichomonas* spp., *Entamoeba* spp.), or for *Shigella* spp. or *E coli*, and who showed leukocytes in the stool samples had a more rapid recovery of body weight (median, 10% of body weight; range, 7% to 13%) than did the 319 patients (10%) whose stool cultures were positive for these pathogens. In the former group, diarrhea was probably due to a viral infection. Metronidazole (for treatment at home) was prescribed for the 319 patients (10%) whose stool cultures were positive for parasites. For the 812 patients (26%) whose stool examinations were positive for leukocytes, trimethoprim-sulfamethoxazole was prescribed.

At reassessment on day 3, rehydration had to be repeated in 2% of patients in group B, 3% in group C, and no patients in group A ($P < 0.001$). Group A also showed better compliance to treatment.

DISCUSSION

This study determined the efficacy of NGT rehydration with solutions having different osmolarities (high osmolarity [90 mEq/L Na^+], low osmolarity [30 mEq/L Na^+], or both). For European children, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition¹⁰ (ESPGHAN) recommends replacing a solution containing 90 mEq/L Na^+ , 110 mmol/L glucose, 20 mEq/L K^+ , and 10 mEq/L NaHCO_3 (ie, the WHO formula³) with a solution containing less Na^+ (60 mEq/L), partially in the form of trisodic citrate. The composition of the available rehydration solution products, the solution recommended by ESPGHAN, and our 2 formulas are reported in Table VI. Our study demonstrates that, in this part of western Africa, a lower Na^+ content can be used effectively because the *V cholera* infection is uncommon and results in a lower loss of Na^+ in the stool than in patients infected with *V cholera*. We developed a rehydration strategy that provided a higher osmolarity solution at the beginning of rehydration, followed by a lower osmolarity solution. The use of a solution with a lower Na^+ content and the same glucose content represents an important step before starting refeeding, thus reducing the risk for hypoglycemia (which typically occurs immediately before refeeding).

Table VI. Commercially available (in Europe) rehydration solutions and their compositions compared with the ideal solution for European children as recommended by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and with the 2 high- and low-osmolality solutions used in this study.

Solution	Glu ^a	Na ⁺ , mEq/L	K ⁺ , mEq/L	Cl ⁻ , mEq/L	NaHCO ₃ , mEq/L	Other Anions, mEq/L	Osmolality, mOsm/L	Glu/Na ⁺ Ratio
Brand name								
Alhydrate ^{®b}	80 g/L ^c	60	20	60	0	18	300	0.0
Amidral ^{®d}	47 g/L ^e	60	20	60	20	0	167	0.0
Dicodral 60 ^{®d}	90	60	20	37	0	14	221	1.5
Dicodral Liquid ^{®d}	110	30	20	40	10	0	210	8.2
Dicodral Strong ^{®d}	110	90	20	80	30	0	330	1.2
Equidral ^{®f}	^g	60	20,44	28,66	0	18	220	0.0
GES 60 ^{®h}	110	60	20	50	30	0	270	1.8
Idravita ^{®i}	60	60	20	50	0	10	230	1.0
Oralamid ^{®j}	62 g/L ^k	60	20	52	0	12	224	0.0
Pedialyte ^{®l}	250	30	20	30	0	28	247	8.2
Reidral ^{®m}	75	60	20	60	0	30	225	1.2
Reidrax ^{®n}	183	23	9	21	0	11	245	7.9
Sodioral ^{®j}	88	60	20	30	0	50	215	1.5

(continued)

Table VI. (Continued)

Solution	Glu ^a	Na ⁺ , mEq/L	K ⁺ , mEq/L	Cl ⁻ , mEq/L	NaHCO ₃ , mEq/L	Other Anions, mEq/L	Osmolarity, mOsm/L	Glu/Na ⁺ Ratio
ESPGHAN	74–111	60	20	25–60	10	0	200–250	1.2–1.8
Our high-osmolarity formula (90 mEq/L Na ⁺)	110	90	20	80	30	0	310	1.2
Our low-osmolarity formula (30 mEq/L Na ⁺)	110	30	20	40	10	0	210	8.2

Glu = glucose; Na⁺ = sodium electrolyte; K⁺ = potassium electrolyte; Cl⁻ = chloride electrolyte; NaHCO₃ = sodium bicarbonate.

^aValues are expressed in mmol/L unless otherwise noted.

^bNestlé S.A. (Vevey, Switzerland).

^cMixture of saccharose and maltodextrins.

^dDicofarm SpA (Rome, Italy).

^eRice starch.

^fBioTrading® Benelux B.V. (Mijdrecht, the Netherlands).

^gGluco-oligosaccharides.

^hMilupa GmbH and Co. KG (Friedrichsdorf, Germany).

ⁱHumana (Milan, Italy).

^jGlDaGROUP® Pharmaceuticals (Adelaide, Australia).

^kMixture of glucose, corn starch, and vegetables.

^lAbbott Laboratories (Abbott Park, Illinois).

^mBonomelli sir (Dolzago, Italy).

ⁿEG S.p.A. (Milan, Italy).

At the end of hydration, 90% of patients who were receiving hydration at lower osmolality had no edema due to hypernatremia, were less lethargic, and were better able to tolerate the initial refeeding. The patients who received rehydration with a high-osmolality solution via NGT had higher serum Na^+ concentrations than did those who had received rehydration fluid with a low-osmolality solution.

The efficacy of a low-osmolality ORS (glucose and salt content reduced to 75 to 90 mmol/L and 60 to 75 mEq/L, respectively [total osmolality, 225 to 245 mOsm/L]), has been demonstrated in several studies.¹¹⁻¹⁴ ORS significantly reduced stool output and duration of diarrhea, compared with treatment with a standard ORS and the equivalent concentration of glucose (75 mmol/L) and Na^+ (75 mEq/L). Maintaining the osmolality at 245 mOsm/L is essential to facilitate Na^+ absorption.

In these studies,¹¹⁻¹⁴ patients who received ORS with reduced osmolality may have had an increased risk for hyponatremia (defined as a serum Na^+ concentration <130 mEq/L) after 24 hours of treatment, but this result was of no clinical significance. The incidence of vomiting in patients given reduced-osmolality (75 mEq/L Na^+ , 75 mmol/L glucose, and a total osmolality of 245 mOsm/L) ORS was significantly reduced (~30%), but the incidence of hyponatremia did not differ significantly from that in the patients receiving standard ORS solution. Reduced-osmolality ORS was effective in patients infected with *V cholera*, who have an increased risk for transient, asymptomatic hyponatremia. However, in future studies, further monitoring is required to better assess this risk.

Our study suggests that, in countries where infection with *V cholera* is not likely to be the cause of diarrhea, it is preferable to start with a solution of 90 mEq/L Na^+ followed by a solution of 30 mEq/L Na^+ . In our study, this treatment appeared to prevent hyponatremia and shock in all the patients who received it. However, the programmatic and logistic advantages of using a single, low-osmolality solution worldwide for all causes of diarrhea and in patients of all ages would surely represent the gold standard in the treatment of diarrhea.

Pulmonary edema, which may occur when too large a volume of venous fluids is given in an attempt to correct metabolic acidosis, was not observed in our patients. Furthermore, renal failure did not occur when too little fluid was given, when shock was rapidly corrected, and when hydration was maintained according to the guidelines. The lack of adverse events in our study indicates that all 3 treatments were well tolerated.

CONCLUSIONS

In this study, rehydration with the WHO formula and with lower-osmolality solutions was shown to be effective in body weight recovery. Appropriate refeeding also is recommended in treating diarrhea, with the addition of milk in Western countries and preferably with complex carbohydrates in countries

such as Burkina Faso, where millet, soybeans, and peanuts are the main components of the diet. This study supports the revision of oral rehydration concepts both in developed countries and in the rest of the world, by reducing the osmolality of the WHO rehydration solution.

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