

# Standard WHO-ORS Versus Reduced-osmolarity ORS in the Management of Cholera Patients

Sri Pandam Pulungsih<sup>1</sup>, Narain H. Punjabi<sup>2</sup>, Kustedy Rafli<sup>1</sup>, Atti Rifajati<sup>1</sup>,  
Swiandy Kumala<sup>1</sup>, Cyrus H. Simanjuntak<sup>3</sup>, Yuwono<sup>4</sup>, Murad Lesmana<sup>5</sup>,  
Decy Subekti<sup>2</sup>, Sutoto<sup>†1</sup>, and Olivier Fontaine<sup>6</sup>

<sup>1</sup>Infectious Diseases Hospital Prof. Dr. Sulianti Saroso, Jakarta, Indonesia (†Dr. Sutoto passed away in 2003), <sup>2</sup>U.S. Naval Medical Research Unit No. 2, Jakarta, <sup>3</sup>National Institute of Health Research and Development, Jakarta, <sup>4</sup>Directorate General of Center for Disease Control and Environmental Health, Ministry of Health, Jakarta, <sup>5</sup>Medical Faculty, Trisakti University, Jakarta, and <sup>6</sup>Department of Child and Adolescent Health and Development, World Health Organization, Geneva 27, Switzerland

## ABSTRACT

The study compared the safety and efficacy of an oral rehydration salts (ORS) solution, containing 75 mmol/L of sodium and glucose each, with the standard World Health Organization (WHO)-ORS solution in the management of ongoing fluid losses, after initial intravenous rehydration to correct dehydration. The study was conducted among patients aged 12-60 years hospitalized with diarrhoea due to cholera. One hundred seventy-six patients who were hospitalized with acute diarrhoea and signs of severe dehydration were rehydrated intravenously and then randomly assigned to receive either standard ORS solution (311 mmol/L) or reduced-osmolarity ORS solution (245 mmol/L). Intakes and outputs were measured every six hours until the cessation of diarrhoea. During maintenance therapy, stool output, intake of ORS solution, duration of diarrhoea, and the need for unscheduled administration of intravenous fluids were similar in the two treatment groups. The type of ORS solution that the patients received did not affect the mean serum sodium concentration at 24 hours after randomization and the relative risk of development of hyponatraemia. However, patients treated with reduced-osmolarity ORS solution had a significantly lower volume of vomiting and significantly higher urine output than those treated with standard WHO-ORS solution. Reduced-osmolarity ORS solution was as efficacious as standard WHO-ORS solution in the management of cholera patients. The results indicate that reduced-osmolarity ORS solution is also as safe as standard WHO-ORS solution. However, because of the limited sample size in the study, the results will have to be confirmed in trials, involving a larger number of patients.

**Key words:** Diarrhoea; Cholera; Oral rehydration solutions; Rehydration; Dehydration; Osmolar concentration; Randomized controlled trials; Double-blind method; Comparative studies; Indonesia

## INTRODUCTION

The discovery of oral rehydration salts (ORS) solution for the treatment of dehydration due to diarrhoea is considered to be one of the greatest achievements of medical research in the 20th century (1). Since it was recommended by the World Health Organization (WHO) in

1978 for the management of all types of diarrhoea in all age-groups, numerous studies have been undertaken to develop an 'improved' ORS. The goal was to discover a product that would be at least as safe and effective as standard ORS solution for preventing or treating dehydration from all types of diarrhoea but which, in addition, would reduce stool output or have other important clinical benefits. One approach has emphasized reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing glucose and salt (NaCl) concentrations in the solution (2-10). Results of studies conducted on

Correspondence and reprint requests should be addressed to:  
Dr. Narain H. Punjabi  
U.S. Naval Medical Research Unit No. 2  
Jakarta 10560  
Indonesia  
Email: narain@namru2.org  
Fax: (62-21) 420-7854/424-4507

children with non-cholera diarrhoea and comparison of this reduced-osmolarity ORS solution with the standard WHO-ORS solution showed that reduced-osmolarity ORS solution significantly reduced stool output, vomiting, and the need for unscheduled intravenous infusion (7). Besides, reduced-osmolarity ORS solution also significantly decreased mean serum sodium concentration at 24 hours. However, all cases of hyponatraemia reported in these studies were asymptomatic. Based on these results, it appears that reduced-osmolarity ORS solution, containing a reduced amount of sodium and glucose, had beneficial effects on the clinical course of diarrhoea and is as safe as the standard WHO-ORS solution for use in acute infantile diarrhoea (7).

These results, however, raised some concerns about the safety and efficacy of using reduced-osmolarity ORS solution for the treatment of cholera patients as the faecal concentration of sodium is higher in cholera than in non-cholera diarrhoea (7). A reduced-osmolarity ORS solution, containing 75 mmol/L of sodium instead of 90 mmol/L, might not allow full replacement of sodium lost, possibly leading to an increase in ORS intake, an increase in the need for intravenous therapy, and a higher risk of hyponatraemia. We, therefore, conducted a double-blind randomized clinical trial to compare the efficacy and safety of the standard WHO-ORS solution with that of reduced-osmolarity ORS solution in patients (mostly adults) with dehydration due to *Vibrio cholerae* O1.

## MATERIALS AND METHODS

The study was conducted at the Infectious Diseases Hospital (IDH) Prof. Dr. Sulianti Saroso, Jakarta, Indonesia. Patients aged 12 years or older are admitted to the adult ward in this hospital. In this study, patients aged 12-60 years with—(a) acute watery diarrhoea for less than 24 hours prior to admission, (b) clinical signs of severe dehydration according to the WHO guidelines (11), (c) stool output of less than 5 g/kg.h during the initial intravenous infusion, and (d) no visible blood in stool—were enrolled in the study after obtaining verbal consent from patients or from their guardians if they were not in condition to provide consent due to their mental status condition at the time of enrollment in the study. Pregnant women and patients who had systemic infections or other diseases requiring specific additional treatment were excluded. Patients with negative stool/rectal swab culture for *V. cholerae* O1 were also excluded during the final analysis. All patients were initially treated with intravenous infusion with Ringer's lactate solution given at a rate of 110 mL/kg plus replacement of ongoing losses,

until blood pressure and pulse returned to normal and they were able to tolerate oral fluids. This procedure usually takes 6-8 hours at the IDH, Jakarta, and is slower than in other rehydration centres. After initial intravenous rehydration and provided they met the inclusion criteria, these patients were enrolled in the study and randomly assigned to one of the two treatment groups—reduced-osmolarity ORS solution or standard WHO-ORS solution (Table 1). The randomization list was established at the WHO in Geneva, with random permuted blocks of variable length (6-12 subjects per block). The packets of reduced-osmolarity ORS solution and of standard ORS solution, identical in appearance and packaged in identical sachets, were arranged in a sequence corresponding to the master randomization code, numbered sequentially, and then sent to Indonesia. Fifteen packets were assigned to each patient. Rehydration therapy was conducted with the assigned ORS solution on

**Table 1.** Composition of oral rehydration solutions

Composition	Reduced-osmolarity ORS*	Standard WHO-ORS†
Glucose (mmol/L)	75	111
Sodium (mmol/L)	75	90
Potassium (mmol/L)	20	20
Chloride (mmol/L)	65	80
Citrate (mmol/L)	10	10
Osmolarity (mmol/L)	245	311

\*Dispensed in powder form with the following ingredients (all measured in g/L): sodium chloride—2.6, trisodium citrate—2.9, potassium chloride—1.5, and glucose—13.5  
 †Dispensed in powder form with the following ingredients (all measured in g/L): sodium chloride—3.5, trisodium citrate—2.9, potassium chloride—1.5, and glucose—20  
 ORS=Oral rehydration solution; WHO=World Health Organization

an *ad-libitum* basis, with the minimum amount administered equal to replacement of ongoing losses (watery or loose stools and vomit) until diarrhoea stopped (defined as the start of the first 12-hour period during which no diarrhoeal stool passed). Plain water was also freely available. Immediately after completion of rehydration, patients in both the groups were offered food (noodles). Thereafter, meals were provided three times a day throughout the study period.

The indication for giving supplemental intravenous fluids during the course of the trial was re-appearance of signs of severe dehydration despite administration of

appropriate ORS solution. These patients were given rapid intravenous infusion with Ringer's lactate solution to correct all the signs of dehydration within 2-3 hours. The patients then resumed treatment with their assigned ORS solution and were kept into the study. All patients admitted to the study received tetracycline, 500 mg four times a day for two days. The first dose of antibiotic was given with the initiation of ORS therapy.

All intakes and outputs were measured and recorded every six hours until the cessation of diarrhoea, or withdrawal from the study. Stool output was measured using cholera cots and buckets placed below the cholera cots. Every six hours the buckets were emptied, and the volume of stool in it was measured and recorded. Patients were also given urinal for urine and were requested to use it for urination. They also were given a special smaller bucket to be used if they vomited; the bucket was also emptied every six hours and the volume measured and recorded. Clinical assessment of patients, number and characteristics of stools passed, and number and volume of vomiting episodes were recorded continuously and summarized for a six-hour period. Body-weight was recorded on admission, after rehydration, and then every 24 hours until discharge.

Blood samples were obtained on admission, after completion of intravenous rehydration, and 24 hours later for measurement of serum sodium and potassium concentrations by standard methods (12). Rectal swab and stool samples were collected from each study patient at the time of admission. These samples were inoculated into Cary-Blair media for transport to the laboratory, where they were processed by standard methods for the isolation of *V. cholerae* O1, which included inoculation onto the following agar plating media: thiosulfate-citrate bile salts agar, deoxycholate-citrate lactose saccharose agar, *Salmonella-Shigella* agar, and MacConkey agar (13,14). The study was designed to detect a 30% difference in total stool output between the treatment groups.

On the basis of results of a study conducted among similar patients in the same hospital, we calculated that 56 patients with culture-proven cholera per group would be needed to show this difference with a type II error of 0.20 and a type I error of 0.05 (15). In our previous studies, 80% of patients fulfilling the above inclusion criteria were shown to harbour *V. cholerae* in their stools. Therefore, we decided to admit 80 patients per treatment group to recruit at least 60 patients with positive stool culture for *V. cholerae* O1.

The protocol was approved by the ethics committees of the hospital and by the Committee for the Protection

of Human Subjects of NAMRU-2 as study protocol no. 9319 in 1993 and by the Sub Committee on Research Involving Human Subject of the WHO.

Statistical analyses were computed on Epi Info (Centers for Disease Control and Prevention, Atlanta, Georgia, USA, and World Health Organization, Geneva, Switzerland) and SPSS for Windows software (SPSS Inc., Chicago, Ill). A two-tailed Student's *t*-test was used for comparing the groups. The Fisher Exact Test was used for comparing qualitative variables. Kruskal-Wallis One Way was used for analysis of variance. Relative risks were calculated by the Mantel-Haenszel risk ratio (16,17).

## RESULTS

During January 1994–January 1995, 176 patients were enrolled in the study, of whom 160 had a positive stool/rectal swab culture for *V. cholerae* O1 and were included in the final analysis. Seventy-eight patients—38 males and 40 females—were randomly assigned to receive reduced-osmolarity ORS solution and 82 patients—50 males and 32 females—to receive the standard WHO-ORS solution. There were no differences between the treatment groups in characteristics at the time of admission and in stool output during the initial intravenous infusion prior to randomization (Table 2).

Data collected from all 160 patients were included in the final analysis up to the time when diarrhoea stopped. No patients were withdrawn from the study. The treatment groups did not differ in stool output, intake of ORS, duration of diarrhoea, or proportion of patients who required unscheduled intravenous infusion after randomization

**Table 2.** Characteristics of patients on admission

Characteristics	Reduced-osmolarity ORS (n=78) (mean±SD)	Standard WHO-ORS (n=82) (mean±SD)
Age (years) of patients	29±11	27±10
Weight (kg)	46.7±9.7	45.7±7.9
Male:female	38:40	50:32
Duration (hours) of diarrhoea prior to admission	19±14	19±15
Pre-randomization initial rehydration		
Volume of intravenous fluids (mL)	7,446±1,964	7,853±1,968
Stool volume (mL)	2,560±1,051	2,846±1,411

ORS=Oral rehydration solution; SD=Standard deviation; WHO=World Health Organization

in the study. However, urine output in the first 24 hours following randomization was significantly smaller in patients receiving the standard WHO-ORS solution, while vomiting during the same period was significantly reduced in patients receiving reduced-osmolarity ORS solution (Table 3). The mean serum sodium concentration at 24 hours did not differ significantly between the treatment groups (139±7 mEq/L for reduced-osmolarity ORS and 140±10 mEq/L for standard WHO-ORS). The relative risk of development of hyponatraemia (serum Na <125 mEq/L) during the first 24 hours of treatment was not significantly greater in patients who received reduced-osmolarity ORS solution (RR=1.1; 95% CI 0.5-2.7). Two patients in the reduced-osmolarity ORS solution group had hyponatraemia (serum sodium <125 mEq/mL). However, both were asymptomatic until the time of discharge from the hospital. The mean serum potassium concentrations at 24 hours were similar in both the groups (3.1 mEq/L). There were three patients with asymptomatic hypokalaemia (serum potassium <3

mEq/mL); one of them recovered, and two remained with serum K less than 3 mEq/mL at 24-hour measurement. Patients only with positive stool culture for *V. cholerae* O1 were included in the study. About 10% of these patients also had other pathogens (*Escherichia coli*, *Shigella* spp., and *Salmonella* spp.). No examination was conducted for possible viral and parasitological causes of diarrhoea.

## DISCUSSION

Reports from other similar studies as ours showed glucose-based ORS solution containing reduced amounts of glucose and sodium (and thus with a lower osmolarity) to be more efficacious than the standard WHO-ORS solution in acute infantile diarrhoea (3,7). However, because faecal losses of sodium are greater in diarrhoea due to cholera than in non-cholera diarrhoea, the efficacy and safety of oral rehydration solutions containing reduced amounts of sodium in the treatment of patients with cholera have been questioned. The results of our study showed that reduced-osmolarity ORS solution for the maintenance of patients with cholera was as efficacious as the standard WHO-ORS solution, with regard to stool output and duration of diarrhoea.

There are some inherent or unavoidable flaws with the study. Only adults were supposed to be enrolled in the study. However, patients aged 12 years and above are admitted to the study ward of the IDH, and, thus, a few (n=5) patients aged less than 18 years, but with cholera, were also enrolled in the study. Removing these patients from the analysis did not affect the results (data not shown). Another concern is the speed of initial intravenous rehydration therapy performed in our hospital. Although many rehydration centres around the world use a faster rate of intravenous rehydration (2-3 hours), this procedure at the IDH, Jakarta, generally takes 6-8 hours. In general, rehydration is achieved within three hours, and the intravenous line is usually kept in place for a few more hours in case the patient requires re-institution of intravenous rehydration therapy. Feeding of patients enrolled in this study should also be considered. After completion of the initial intravenous rehydration, rehydrated patients generally start to get their appetite back and usually request for some food. Although rice is the staple food for the Indonesians, packets of instant noodles are almost equally popular. Because consumption of rice requires the use of different salted condiments, such as salted fish, we preferred to provide noodles to all patients to ensure uniformity in feeding of patients. Each packet of instant noodles contains around 940 mg (41 mEq) of sodium. Finally, a last problem

**Table 3.** Clinical features of patients after randomization

Variable	Reduced-osmolarity ORS (n=78) (mean±SD)	Standard WHO-ORS (n=82) (mean±SD)
Stool output (mL)		
24 hours after randomization	3792±2844	3894±2190
Total	4551±3251	4450±2712
ORS intake (mL)		
24 hours after randomization	4668±1909	4193±1596
Total	6964±3018	6464±3972
Volume of vomiting (mL)		
24 hours after randomization	173±372	384±690*
Total	206±416	417±769
Urine output (mL)		
24 hours after randomization	1067±540	893±460*
Total	1761±935	1484±893
Patients requiring additional intravenous fluid infusion (%)	20.5	26.8
Duration (hours) of diarrhoea after randomization	44±13	43±14
*p<0.05 ORS=Oral rehydration solution; SD=Standard deviation; WHO=World Health Organization		

concerns the way urine was collected. Each patient was given a urinal to collect urine, and every effort was made to remind the patient to use it and not to urinate into the bucket below the cholera cot. Nevertheless, there is always some possibility that some amount of urine spilled into the stool-collection bucket. Each study patient received a course of tetracycline for only two days, instead of three-day duration, since results of previous studies at the IDH indicated that two-day treatment for cholera patients is sufficient to eradicate the causative organism compared to the standard three-day course as recommended by the WHO (11).

Urine output at 24 hours was significantly higher in patients receiving reduced-osmolarity ORS solution than in those treated with the standard WHO-ORS solution. This suggests that the patients treated with reduced-osmolarity ORS solution received more 'free' water than the patients from the other group—water that had to be eliminated through urine. However, this increased intake of 'free' water did not result in any significant decrease in the mean serum sodium concentration at 24 hours, nor did it result in any increase in the relative risk of developing hyponatraemia. The safety of reduced-osmolarity ORS solution in this study is further confirmed by the fact that the need for unscheduled intravenous fluid therapy was not increased in patients receiving reduced-osmolarity ORS solution when compared with those treated with the standard WHO-ORS solution (20% vs 27%).

Although the study patients were all severely dehydrated on admission and had a large purging rate during the initial intravenous rehydration period ( $>9\pm 3$  mL/kg.h), stool output in both the treatment groups decreased rapidly in the first 24 hours following randomization and the administration of antibiotics effective against *V. cholerae* O1. Therefore, the volumes of intravenous fluid, containing 130 mEq/L of sodium, administered to all patients during the initial intravenous rehydration period were, for most patients, greater than the volumes of ORS solution consumed during the first 24 hours after randomization. The large amounts of sodium received prior to randomization may, therefore, have reduced any impact, which the reduced-osmolarity ORS solution might have had on the serum sodium levels in those patients.

The results of this first study evaluating the efficacy and safety of reduced-osmolarity ORS solution in adult patients with cholera are very encouraging. However, before these can be generalized for all cases of cholera, it will be important to confirm them in studies recruit-

ing a large sample of patients hospitalized with cholera and treated with larger amounts of reduced-osmolarity ORS solution. We know that one such study has been completed in Bangladesh, and its results will be published soon, and another one is underway in Kolkata, India.

#### ACKNOWLEDGEMENTS

The study was supported by grant from the Control of Diarrhoeal Disease Programme, World Health Organization; by the Indonesian Ministry of Health; and by the U.S. Naval Medical Research and Development Command, Navy Department. For their support and encouragement, the authors would like to thank the Director and staff of the medical, nursing, maintenance, laboratory, emergency room, rehydration and adult (C&D) wards of the Infectious Diseases Hospital Prof. Dr. Sulianti Saroso of Jakarta; Prof. Dr. A.A. Loedin, former Head of the National Institute of Health Research and Development (NIHRD), Ministry of Health, Indonesia, the staff of the Bacteriology Laboratory, Center for Infectious Diseases Research NIHRD RI Jakarta and the late Dr. Gandoeng Hartono, former Head of the Directorate General of Communicable Diseases Control and Environmental Health; the Departments of Microbiology, Clinical Investigations and Epidemiology, Data processing, U.S. Naval Medical Research Unit No. 2, Jakarta. The authors would also thank the Department of Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland, for providing the grant and supplies for the study.

#### REFERENCES

1. Water with sugar and salt. *Lancet* 1978;2:300-1.
2. Duggan C, Fontaine O, Pierce NF, Glass RI, Mahalanabis D, Alam NH *et al.* Scientific rationale for a change in the composition of oral rehydration solution. *JAMA* 2004;291:2628-31.
3. Rautanen T, El-Radhi S, Vesikari T. Clinical experience with a hypotonic oral rehydration solution in acute diarrhea. *Acta Paediatr* 1993;82:52-4.
4. El-Mougi M, El-Akkad N, Hendawi A, Asan M, Amer A, Fontaine O *et al.* Is a low-osmolarity ORS solution more efficacious than standard WHO ORS solution? *J Pediatr Gastroenterol Nutr* 1994;19:83-6.
5. International Study Group on Reduced-Osmolarity ORS Solutions. Multicentre evaluation of reduced-osmolarity oral rehydration salts solution. *Lancet* 1995;345:282-5.
6. Santosham M, Fayad I, Zikri MA, Hussein A, Ampousah A, Duggan C *et al.* A double-blind clinical

- trial comparing World Health Organization oral rehydration solution with a reduced osmolarity solution containing equal amounts of sodium and glucose. *J Pediatr* 1996;128:45-51.
7. Hahn S, Kim Y, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review. *BMJ* 2001;323:81-5.
  8. Faruque ASG, Mahalanabis D, Hamadani JD, Zetterström R. Reduced osmolarity oral rehydration salt in cholera. *Scand J Infect Dis* 1996;28:87-90.
  9. Alam NH, Majumder RN, Fuchs GJ, and CHOICE Study Group. Efficacy and safety of oral rehydration solution with reduced osmolarity in adults with cholera: a randomized double-blind clinical trial. *Lancet* 1999;354:296-9.
  10. World Health Organization. International Study Group on Reduced-osmolarity ORS Solutions. Multicentre evaluation of reduced-osmolarity oral rehydration salts solutions. *Lancet* 1995;345:282-5.
  11. World Health Organization. Programme for Control of Diarrhoeal Diseases. The treatment of diarrhoea: a manual for physicians and other senior health workers. Geneva: World Health Organization, 2005: 6-8.
  12. Lynch TJ, Raphael SS, Mellor LD, Spare PD, Inwood MJH, editors. General chemical pathology *In: Medical laboratory technology and clinical pathology*. 2d ed. Philadelphia: Saunders, 1969:379-80.
  13. Tietz NW, Pruden EL, Siggaard-Anderson O. Electrolytes, blood gases and acid base balance. *In: Tietz NW, editor. Fundamentals of clinical chemistry* 3d ed. Philadelphia: Saunders, 1987:614-20.
  14. World Health Organization. Programme for Control of Diarrhoeal Diseases. Manual for laboratory investigations of acute enteric infections. Geneva: World Health Organization, 1987:5-30. (WHO/CDD/83.3 rev.1).
  15. Pocock SJ, editor. The size of a clinical trial. *In: Clinical trials—a practical approach*. Chichester: Wiley, 1987:123-41.
  16. Gardner MJ, Altman DG. Statistics with confidence. London: BMJ Books, 1989:50-63.
  17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.