Paediatrica Indonesiana

VOLUME 49 May • 2009 NUMBER 3

Original Article

Efficacy of reduced osmolarity oral rehydration solution, rice-based oral rehydration solution, and standard WHO oral rehydration solution in children with acute diarrhea – a randomized open trial

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Abstract

Background The composition of the WHO's standard oral rehydration solution (ORS) is similar to that of choleric stool. Currently, there are questions about whether the composition is acceptable for treating dehydration caused by diarrhea. Efforts are being made to try and improve the WHO ORS, e.g., to decrease the solution osmolarity to avoid hypertonic side effects. It is acknowledged that if glucose is used in ORS, the sodium will go through enterocytes and glucose will turn into an absolute substance for the formula. Glucose is less affordable and not widely produced in developing countries, hence researchers are currently exploring substitutes such as rice flour.

Objective To compare the efficacy of reduced osmolarity ORS, rice-based ORS and the WHO standard ORS among children with acute diarrhea.

Methods A randomized open trial was conducted in children aged 6-59 months old admitted for acute diarrhea. One-way ANOVA was used to compare the three different types of ORS given.

Results The mean duration of diarrhea was significantly lower in the group treated with reduced osmolarity ORS (52.66 h, 95% CI 47.13 to 58.18) and rice-based ORS (54.66 h, 95% CI 47.97 to 61.34) compared to the group treated with the WHO standard ORS (67.34 h, 95% CI 61.50 to 73.18). Multivariate analysis shows that intervention had a significant effect on reducing the duration of diarrhea.

Conclusions Reduced osmolarity ORS and rice-based ORS significantly lower the mean duration of children with acute diarrhea compared with the group treated with the WHO standard ORS. **[Paediatr Indones. 2009;49:169-76]**.

Keywords: *acute diarrhea, reduced osmolarity oral rehydration salts, rice-based oral rehydration salts, efficacy*

Diarrhea is the leading cause of childhood morbidity and mortality, accounting for 4.6 million deaths worldwide annually.[1] It is estimated that the overall incidence of acute diarrhea ranges from 1.3 to 2.3 episodes per year for children under five.[2] In 2007 at the Department of Child Health, Sanglah Hospital there were 342 patients with acute diarrhea, with 98% of them were underfives.[3]

Oral rehydration therapy (ORT) is recommended by the American Academy of Pediatrics (AAP) and the World Health Organization (WHO) as first-line therapy for mild to moderate dehydration. However, doctors report several barriers to the use of ORT for dehydration due to acute diarrhea in children.[4,5] For more than 35 years, the WHO recommended a standard glucose-based oral rehydration solution (ORS) with 90

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mMol/L of sodium, 111 mMol/L of glucose, and a total osmolarity 311 mMol/L.[6] This composition is similar to choleric stool. As the incidence of cholera is just 0.6%, questions were asked about whether the composition is acceptable to treat dehydration caused by non-choleric diarrhea. There have been concerns that this original solution, which is slightly hyperosmolar compared to blood plasma, may risk hypernatremia or an increase in stool output, especially in infants and young children. For this reason, pediatricians in some developed countries recommend that the sodium and glucose content of ORS should be reduced to 75 mMol/L with a total osmolarity 245 mMol/L.[7,8] However, some studies have reported a slightly increased risk of hyponatremia in patients who have received this reduced osmolarity ORS.[9]

The combination of salt and sugar probably enhances absorption of fluid because sodium and glucose are coupled when transported in the small intestine; glucose promotes absorption of both sodium ions and water. Glucose is less affordable and not widely produced in developing countries; hence we explored rice flour as substitute.

Methods

A randomized open conducted at the Gastro-Hepatology Division, Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar, from February to May 2008. Eligible patients were selected by means of consecutive sampling. The study was approved by the Ethics Committee of the Medical School, Sanglah Hospital, Denpasar, and informed consent was obtained from parents.

Sample size was calculated using estimation of amount of sample for hypothesis of mean of three population.[10] Based on the calculated sample size [(ϕ=0.3, α=0.05, β=0.20 or power=80%, μ_1=1.7 (mean duration of diarrhea after reduced osmolarity ORS was been given)[11], μ_2=3.2 (mean duration of diarrhea after rice-based ORS was given)[12], μ_3=3.3 (mean duration of diarrhea after WHO standard ORS was given)[11], r=3 (number of intervention), σ=2.01 (mean of variance)], the minimum sample size for this study was 41 for each group, giving a total of 123 study subjects.

The inclusion criteria were subjects with mild to moderate dehydration due to acute diarrhea (WHO Criteria), aged 6 – 59 months, pre-hospital diarrhea was equal to or less than two days, and informed consent was obtained from the parents. Subjects with complicated diarrhea and diarrhea with complication, received symptomatic therapy before admission, or had infectious diarrhea were excluded.

Definitions of variables

Reduced osmolarity ORS contains 75 mmol/L sodium, 10 mmol/L citrate, 20 mmol/L potassium, 50 mmol/L chloride, 75 mmol/L glucose, with total osmolarity 245 mmol/L.[11] Rice-based ORS contains 60 mmol/L sodium, 10 mmol/L citrate, 20 mmol/L potassium, 60 mmol/L chloride, 50 gr rice flour, with total osmolarity 230 mmol/L.[12] The WHO standard ORS contains 90 mmol/L sodium, 10 mmol/L citrate, 20 mmol/L potassium, 80 mmol/L chlorida, 111 mmol/L glucose, with total osmolarity 311 mmol/L.[11]

Acute diarrhea was defined as a frequency of defecation of more than three times/day or more than the usual habit that was accompanied by changes in feces consistency with or without blood and/or mucous lasting for less than seven days. Recovery time was the time needed until the frequency of defecation was equal to or less than three times per day, with normal stool consistency and no complications. Diarrhea with complications was defined as acute diarrhea accompanied by severe dehydration, metabolic acidosis, seizure, paralytic ileus, hypernatremia, hyponatremia, and/or renal failure. Complicated diarrhea was defined as acute diarrhea with severe malnutrition, dysentery-type diarrhea, diarrhea with others illness such as acute respiratory infection, anemia, measles, deficiency of vitamin A, heart diseases, and/or congenital anomaly of gastrointestinal system. Dehydration status was assessed according to the WHO standard[5,6] and nutritional status was measured with standardized anthropometry according to CDC NCHS-WHO 2000 and classified based on the Waterlow criteria.[13]

Efficacy of the treatment was measured by assesing the duration of diarrhea (h) as a primary outcome. Secondary outcomes that were measured in this study were the time needed for frequency of defecation to become less or equal to three times

per day (h), the time needed for stool consistency to become solid or semi solid (h), the time needed for vomiting to disappear (h), the volume of intake of ORS (mL/kgBW), weight gain (g), serum sodium consentration (mmol/L). Hypernatremia was defined as a serum sodium concentration of more than 145 mmol/L.[14] Hyponatremia was defined as a serum sodium concentration of less than 135 mmol/L.[14] Serum sodium concentration was measured at the Clinical Laboratory of Sanglah Hospital on admission and after recovery.

Subjects who requested to be discharged or refused to continue the study were considered as drop-out cases. Treatment failure was defined as a failure to recover by day five of treatment, subjects that experienced complications before day five, had a co-infection, had profuse diarrhea vomiting, or had adverse events that affected the duration of diarrhea.

Study protocol

A questionnaire was used to record the baseline characteristics of the study subjects and the outcome of the study. The study subjects were randomized into three groups using 6-block randomization; group A then received reduced-osmolarity ORS, group B then received rice-based ORS, and group C then received standard WHO ORS. The ORS were prepared packed in similar sachets by the Farmation of Technology Laboratory, Farmation of Faculty, Sanata Dharma University, Yogyakarta. All medicines prescribed before admission were stopped. All study subjects were followed-up until they recovered. To assess the treatment efficacy, we performed measurement of dehydration status and recorded frequency of defecation, stool consistency, total intake of ORS volume, vomiting, adverse events and complications after 3 hours, 12 hours, and then every 24 hours. Measurement of body weight was done on admission and after recovery. Serum sodium concentration was measured on admission and after recovered by the Clinical Laboratory of Sanglah Hospital. Stool specimens were examined microscopically to look for ova, cysts and/or parasites at the Clinical Laboratory of Sanglah Hospital. In this study, drop out and treatment failure rates were accepted if the rate was below 20%. Subjects which were considered as drop out cases or treatment failure were analyzed with the worst assumption to intention to treat analysis.

Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the three groups. Additional variables i.e., complications or adverse events during the study, were analyzed using the X^2 test. The primary outcome result, i.e., the difference in duration of diarrhea between different groups was analyzed using a Kaplan-Meier curve. Differences in duration of diarrhea between two groups were tested using the log-rank test. We made adjustments for external variables in duration of diarrhea between two groups using Cox-regression analysis. A P value of <0.05 with a 95% confidence interval was considered as statistically significant.

Results

During the study period, 143 subjects aged 6-59 months old with acute diarrhea were admitted to the Gastro-Hepatology Division, Department of Child Health, Sanglah Hospital. One-hundred and twenty-three were eligible, enrolled and completed the study while 20 subjects were excluded (10 had other illnesses and 10 had received symptomatic therapy before admission). The subjects were divided into 3 groups that then received a different type of ORS. Baseline characteristics of the study subjects in the three groups were comparable (**Table 1**).

The comparison of primary and secondary outcomes between the three groups are shown in **Table 2**.

Next we performed Kaplan-Meier analysis. The duration of diarrhea for group A (median survival time was 50.00 h, 95% CI 45.55 to 54.45) was significantly shorter (log-rank test, P=0.0157) than group C (median survival time was 68.00 h, 95% CI 58.59 to 77.41 and mean survival time was 67.37 h, 95% CI 61.69 to 73.04). The duration of diarrhea for group B (median survival time was 50.00 h, 95% CI 43.73 to 56.27) was also significantly shorter (log-rank test, P=0.0016) than for group C (median survival time was 68.00 h, 95% CI 58.59 to 77.41 and mean survival time

Table 1. Baseline characteristics of the study subjects

Characteristic	Group A (n=41)	Group B (n=41)	Group C (n=41)
Age, mean (SD) mo	18.8 (13.6)	17.3 (8.53)	19.4 (14.08)
Sex; boys, n (%)	21 (51)	26 (63)	21 (51)
IBW, mean (SD) kg	9.7 (3.45)	10.1 (3.11)	9.7 (3.48)
OBW, mean (SD) kg	10.3 (3.41)	10.5 (3.09)	9.9 (3.46)
Nutritional status			
Good, n (%)	37 (90)	39 (95)	38 (93)
Moderate malnutrition, n (%)	4 (10)	2 (5)	3 (7)
Pre-hospital diarrhea (hours), mean (SD)	19.3 (6.77)	19.7(6.14)	18.2 (6.32)
Frequency/day of pre-hospital diarrhea, mean (SD)	6.7 (1.33)	6.1 (1.4)	6.6 (1.36)
Diet intake, n (%)			
Breast-fed	3 (7)	2 (5)	4 (10)
Breast-fed + Formula-fed + Additional food	7 (17)	4 (10)	6 (15)
Breast-fed + Additional food	13 (32)	10 (25)	10 (25)
Formula-fed + Additional food	6 (15)	15 (37)	8 (20)
Additional food	12 (29)	10 (24)	13 (32)
Pre-hospital symtomatic therapy, n (%)	38 (93)	38 (93)	37 (90)
Serum sodium concentration on admission, mean (SD) mmol/L	135.0 (3.82)	136.7 (3.54)	134.0 (3.53)
Serum sodium concentration on recovery, mean (SD) mmol/L	136.7 (3.09)	138.2 (2.71)	137.2 (2.28)

IBW: In Body Weight (Body weight on admission), OBW: Out Body Weight (Body weight after recovery)

Table 2. Primary and secondary outcomes for the study subjects

Outcome	Group A (n=41)	Group B (n=41)	Group C (n=41)
Primary outcome:			
Duration of diarrhea, mean (SD) h	52.7 (17.50)	54.7 (21.18)	67.3 (18.49)
Secondary outcomes:			
Time for frequency of defecation tobecome normal, mean (SD) hr	52.4 (17.65)	53.5 (20.01)	65.0 (17.76)
Time for stool consistency become normal, mean (SD) hr	50.4 (16.13)	52.7 (20.75)	65.5 (17.54)
ORS intake, mean (SD) ml/kgBW	329 (90.75)	341.7 (97.48)	397.0 (97.44)
Increase in body weight, mean (SD) g	0.6 (0.25)	0.4 (0.15)	0.2 (0.09)
Time for vomiting to disappear, mean (SD) hr	15.8 (16.13)	18.1 (13.98)	29.5 (22.92)
Increase in serum sodium concentration (mmol/L)	1.7 (1.39)	1.5 (1.35)	3.1 (1.71)

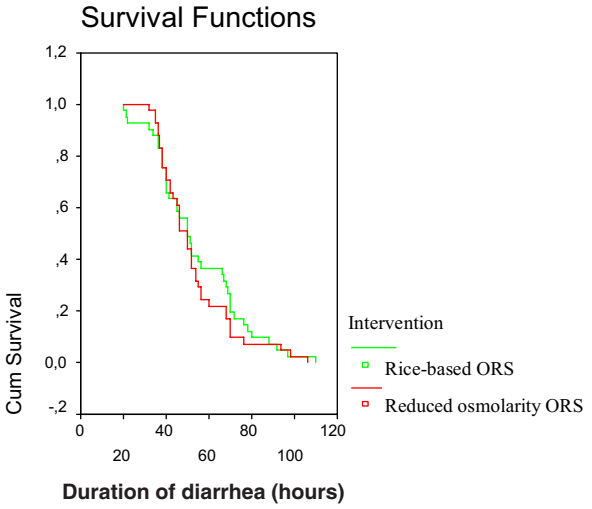

Figure 1. Kaplan - Meier survival curve between group A and B for duration of diarrhea on day 5 of the study

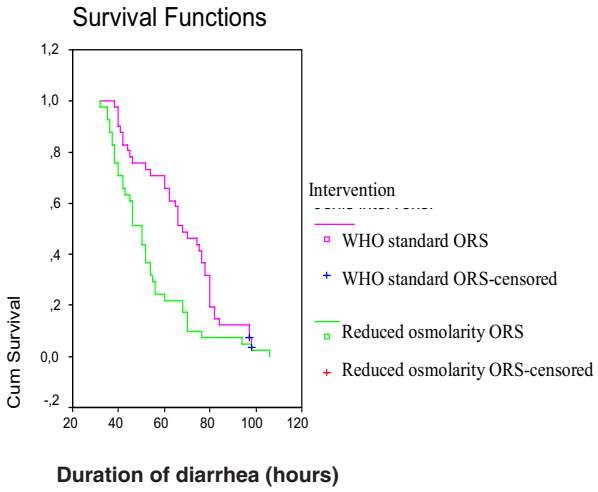

Figure 2. Kaplan - Meier survival curve between group A and C for duration of diarrhea on day 5 of the study

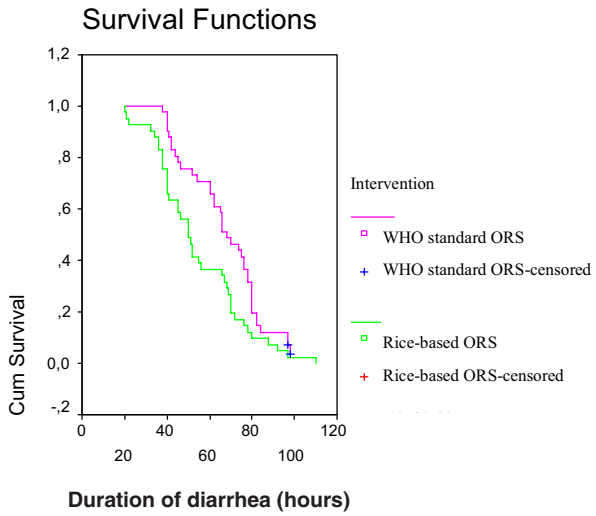

Figure 3. Kaplan - Meier survival curve between group B and C for duration of diarrhea on day 5 of the study

was 67.37 h, 95% CI 61.69 to 73.04). Although duration of diarrhea for group A was shorter (mean survival time was 52.66 h, 95% CI 47.30 to 58.02) than group B (mean survival time was 54.66 h, 95% CI 48.17 to 61.14), this result was not statistically significant (log-rank test, P=0.5250).

Multivariate analysis using XXX was carried out to identify factors that may affect the duration of diarrhea. Type of ORS given was included, as well as age, dietary intake, nutritional status, pre-hospital diarrhea, and symptomatic therapy before admission. It was shown that only the type of ORS given influenced the duration of diarrhea. More specifically, reduced osmolarity ORS and rice-based ORS affected the duration of diarrhea when compared with WHO ORS (Cox Regression, P=0.001 for group A vs. group C, **Table 4** ; P=0.014 for group B vs. group C, (**Table 5**). There was no significant difference between group A and group B (Cox Regression, P=0.440, **Table 3**).

Table 3. Cox Regression analysis to identify variables that affect acute diarrhea duration between group A and group B

Free Variable	B	SE	P	Exp(B)	95% CI for Exp(B)
Age	0.023	0.021	0.283	1.023	0.981 to 1.066
Pre-hospital diarrhea duration	-0.041	0.020	0.065	0.960	0.922 to 0.999
Diet intake					
Breast-fed	1.322	0.805	0.101	3.751	0.774 to 8.176
Breast-fed + Formula-fed + Additional food	0.271	0.574	0.637	1.311	0.425 to 4.042
Breast-fed + Additional food	0.076	0.505	0.880	1.079	0.401 to 2.905
Formula-fed + Additional food	0.754	0.442	0.088	2.126	0.894 to 5.057
Nutritional Status	0.091	0.528	0.863	1.095	0.389 to 3.082
Symtomatic therapy before admission	-0.119	0.412	0.772	0.887	0.396 to 1.990
Oral rehydration solution	-0.189	0.244	0.440	0.828	0.513 to 1.336

B= coeficient cox regression, SE= Standard Error, P= probability Exp(B)= OR, 95% CI= 95% confidence interval

Table 4. Regression analysis to identify variables that affect acute diarrhea duration between group A and group C

Free Variable	B	SE	P	Exp(B)	95% CI for Exp(B)
Age	0.015	0.015	0.320	1.015	0.986 to 1.045
Pre-hospital diarrhea duration	-0.014	0.019	0.444	0.986	0.950 to 1.023
Diet intake					
Breast-fed	0.626	0.633	0.322	1.871	0.541 to 6.472
Breast-fed + Formula-fed + Additional food	0.103	0.503	0.838	1.108	0.414 to 2.970
Breast-fed + Additional food	0.343	0.439	0.434	1.410	0.596 to 3.336
Formula-fed + Additional food	0.365	0.451	0.418	1.441	0.595 to 3.490
Nutritional Status	0.103	0.419	0.806	1.108	0.488 to 2.518
Symptomatic therapy before admission	0.076	0.387	0.844	1.079	0.505 to 2.306
Oral rehydration solution	-0.421	0.129	0.001	0.656	0.510 to 0.844

B= coeficient cox regression, SE= Standard Error, P= probability Exp(B)= OR, 95% CI= 95% confidence interval

Table 5. Regression analysis to identify variables that affect acute diarrhea duration between group B and group C

Free Variable	B	SE	P	Exp(B)	95% CI for Exp(B)
Age	-0.015	0.020	0.472	0.986	0.947 to 1.025
Pre-hospital diarrhea duration	0.004	0.020	0.844	1.004	0.966 to 1.044
Diet intake					
Breast-fed	-0.170	0.756	0.823	0.844	0.192 to 3.717
Breast-fed + Formula-fed + Additional food	-0.181	0.561	0.746	0.834	0.278 to 2.503
Breast-fed + Additional food	-0.824	0.528	0.119	0.439	0.156 to 1.236
Formula-fed + Additional food	-0.401	0.447	0.369	0.669	0.279 to 1.607
Nutritional Status	-0.285	0.489	0.560	0.752	0.288 to 1.963
Symptomatic therapy before admission	0.264	0.423	0.532	1.303	0.568 to 2.986
Oral rehydration solution	-0.620	0.253	0.014	0.538	0.327 to 0.884

B= coeficient cox regression, SE= Standard Error, P= probability Exp(B)= OR, 95% CI= 95% confidence interval

Discussion

We found that reduced-osmolarity ORS and rice-based ORS were more effective than standard WHO-ORS for first-line treatment of children with diarrhea. One explanation for this result might be the hypotonicity of the reduced-osmolarity ORS and rice-based ORS in comparison with the WHO-ORS. A hypotonic solution with low osmolarity containing 60 mmol/L sodium and 50-100 mmol/L glucose and with a total osmolarity ranging from 200-250 mmol/L is more easily absorbed than an isotonic or hypertonic solution.[14,23]

In this study, we compare the efficacy of reduced osmolarity ORS, rice-based ORS, and standard WHO-ORS, as measured based on the primary outcome of duration of diarrhea. The result of our study indicated that the duration of diarrhea in group A was shorter than group B. Some other studies that examined the duration of diarrhea and compared the efficacy of reduced osmolarity ORS and standard WHO-ORS gave similar results to this study.[7,11] However, other studies have given different results such as Rautanen,[15] where the length of diarrhea was shorter in the group that was given reduced osmolarity ORS compared to that of the group given standard WHO-ORS. This may have occurred because the number of subjects was too limited in the XXtudy.

Some studies that compared the efficacy of rice-based ORS and standard WHO-ORS also had similar results to our study, in that rice-based ORS was more effective than WHO-ORS.[17-19] However, Iyngkaran and Yadaf[12] showed that there was no significant difference between these two treatment groups when the age of the subjects was less than six months old. This supports the hypothesis that rice-based ORS can be more useful than standard WHO-ORS in neonatal and older babies.

The time needed for frequency of defecation become less than or equal to three times a day, the time needed for stool consistency to become solid or semi solid, and the time needed for vomiting to cease was significantly shorter ($P<0.0001$) in groups A and B compared with group C. The total volume of ORS intake was less in the reduced osmolarity ORS group (328.97 ml; 95% CI 300.32 to 357.61) and rice-based ORS group (341.73 ml; 95% CI 310.96 to 372.49) compared to the group given WHO standard ORS (397.05 ml; 95% CI 366.29 to 427.81). This result is similar to results from previous studies.[7,11] There was also better body weight recovery for healthy patients in groups A and B compared to group C [0.56 g (95% CI 0.48 to 0.64), 0.45 g (95% CI 0.40 to 0.49) and 0.23g (95% CI 0.22 to 0.28) respectively with $P<0.0001$]. Similar results were also obtained in a study by Bhan[16].

There are concerns about side effects of reduced osmolarity ORS and rice-based ORS such as the occurrence of hyponatremia. One study revealed symptomatic hyponatremia in 0.05% (95% CI 0.03 to 0.07) of children aged $\leq$ 36 months with acute diarrhea who were treated with reduced osmolarity ORS.[9] However, in this study there was no evidence of hyponatremia in any of the three treatment groups.

In some studies, hypernatremia occurs as a result of incorrect use of standard WHO-ORS for treatment of acute diarrhea. Ten percent of subjects with acute diarrhea treated with standard WHO-

ORS in a study by Fayad[21] in Cairo suffered from hypernatremia. Segeren[22] stated that hypernatremia may occurs as a result of incorrect standard WHO-ORS treatment nine times higher [OR=9.12 (95% CI 2.91 to 28.87)]. Even though there was a significant increase in sodium serum level after standard WHO-ORS treatment compare to the other treatments in our study, there was no hypernatremia in any of the three treatment groups. Hypernatremia causes the movement of intracellular liquid to the extracellular compartment in order to maintain plasma osmotic pressure. This can cause cerebral dehydration and shrinking of cells that can develop into venous sinus thrombosis and cause infarction and intracranial bleeding.[23]

By the end of the study period there was one drop-out case group A, one drop-out from group B, and two subjects who experienced treatment failure from group C as they had more than seven days of diarrhea. To uphold the study validity, performed intention to treat analysis was analyzed on all study subjects including the drop-out cases and those with treatment failure by taking worst assumption of treatment result to that subject.

One weakness of this study is that blinding of subjects cannot be performed because rice-based ORS looks different from the other ORS treatments after dissolving in water. We attempted to resolve this matter by packaging all treatments in the same way.

In conclusion, reduced osmolarity ORS and rice-based ORS are beneficial for the management of acute diarrhea in infants as they shorten the length of the period of diarrhea. In addition, these treatments are safe.

Acknowledgments

Our highest respect and gratitude to Head of Faculty of Pharmacy Sanata Dharma University, Yogyakarta, and all staff for their support and assistance in accommodating use of reduced osmolarity ORS, rice-based ORS, and standard WHO ORS.

Our highest respect and gratitude to all staff and paramedics at the Department of Child Health, Udayana University, Sanglah Hospital, Denpasar for supporting this study, and to all subjects and their families who participated in this study.

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