Symptomatic Hyponatremia During Treatment of Dehydrating Diarrheal Disease With Reduced Osmolarity Oral Rehydration Solution

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Context  In May 2002, the World Health Organization and the United Nations Children’s Fund recommended that the formulation of oral rehydration solution (ORS) for treatment of patients with diarrhea be changed to one with a reduced osmolarity and that safety of the new formulation, particularly development of symptomatic hyponatremia, be monitored.

Objective  To measure the rates of symptomatic hyponatremia during treatment of patients with diarrhea with reduced osmolarity ORS.

Design, Settings, and Patients  A phase 4 trial conducted at the Dhaka hospital (December 1, 2002- November 30, 2003) and Matlab hospital (February 2, 2003-January 31, 2004) of the International Centre for Diarrhoeal Disease Research Bangladesh: Centre for Health and Population Research, Dhaka, Bangladesh. All patients admitted with uncomplicated watery diarrhea were treated with the newly recommended ORS and monitored. Patients developing neurological symptoms (seizure or altered consciousness) were transferred to the special care ward for treatment and investigated to identify the cause of the symptoms. Patient records of the Dhaka hospital were reviewed during the previous year when the old ORS formulation was used.

Intervention  Reduced osmolarity ORS.

Main Outcome Measure  Incidence rate of symptomatic hyponatremia in a 1-year period.

Results  A total of 53,280 patients, including 22,536 children younger than 60 months, were monitored at the Dhaka and Matlab hospitals. Twenty-four patients, none older than 36 months, developed seizures or altered consciousness associated with hyponatremia, with an overall incidence rate of 0.05% (95% confidence interval [CI], 0.03%-0.07%) at the Dhaka hospital and 0.03% (95% CI, 0.01%-0.09%) at the Matlab hospital. During the previous year, 47 patients at the Dhaka hospital had symptoms associated with hyponatremia, for an estimated incidence rate of 0.10% (95% CI, 0.07%-0.13%). The reduction in the rates was statistically significant (odds ratio, 0.50; 95% CI, 0.29-0.85; \( P = .009 \)).

Conclusion  The risk of symptoms associated with hyponatremia in patients treated with the reduced osmolarity ORS is minimal and did not increase with the change in formulation.

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is slightly hyperosmolar relative to plasma, might induce development of hypernatremia or an osmotically driven increase in stool output, especially in infants and young children.6-8 For this reason, pediatricians in some developed countries recommended that the sodium content of ORS be reduced to 60 mEq/L, with a total osmolarity of 250 mOsm/L.7 (In the United States, the leading brands have an even lower sodium and a higher glucose concentration, and therefore do not conform to the WHO recommendations.)

Recent efforts to improve the efficacy of ORS have focused on solutions with reduced osmolarity (range of sodium, 60-75 mEq/L and range of glucose, 1351-1622 mg/dL [75-90 mmol/L]).6 These solutions generally preserve the 1:1 molar ratio of sodium to glucose that is crucial for efficient cotransport of sodium but present a lower osmolar load to the intestinal tract than the old formula did. Animal and human studies indicate that such solutions might be better designed for optimal water and electrolyte transport into the blood stream. In these intestinal perfusion studies, solutions with reduced osmolarity have been demonstrated to have improved net water absorption and equivalent net sodium absorption compared with standard ORS.

A number of clinical trials have been performed in children with acute noncholera diarrhea and in children and adults with cholera.6,14,17 The results of these trials were reviewed in a meeting of experts held in New York on July 18, 2001 and summarized in an independent meta-analysis involving 15 studies and 2397 patients.15 The meta-analysis concluded that, "In children admitted to hospital with dehydration associated with diarrhea, reduced osmolality rehydration solution is associated with reduced need for unscheduled intravenous infusions, lower stool volume, and less vomiting compared with standard WHO rehydration solution." Similarly, the expert meeting concluded, "For adults with cholera, a reduced osmolality ORS solution with 75 mmol/L of sodium and 75 mmol/L of glucose is as effective as standard WHO/UNICEF ORS solution." However, some patients with severely purging cholera in an earlier trial that used a solution with 67 mEq/L of sodium did develop asymptomatic hyponatremia and, thus, some concern remained about the possible risk of symptomatic hyponatremia with a 75-mEq/L solution. This concern was not considered sufficient to prevent the use of this solution to treat adults with cholera. It was agreed, however, that the incidence of symptomatic hyponatremia in patients should be monitored when the reduced osmolarity ORS was first introduced for routine use. This conclusion was confirmed in a recently published Cochrane meta-analysis.

Following this recommendation, the International Centre for Diarrhoeal Disease Research Bangladesh (ICDDR,B): Centre for Health and Population Research, Dhaka, Bangladesh, decided to (1) introduce the new ORS formulation for routine use at its Dhaka (urban) and Matlab (rural) hospitals for treatment of patients with diarrhea, and (2) to conduct surveillance (phase 4 study) to monitor the occurrence of symptomatic hyponatremia (altered consciousness, seizures, or both associated with biochemical hyponatremia) or other unexpected events while using the new formulation.

**METHODS**

**Study Sites**
The study was performed at the Dhaka and Matlab hospitals of ICDDR,B: Centre for Health and Population Research over a complete 1-year period (December 1, 2002–November 30, 2003, at the Dhaka hospital and February 2, 2003–January 31, 2004, at the Matlab hospital). Both hospitals have short stay wards in which patients who have diarrhea are admitted for rehydration. The average stay is less than 24 hours. Patients who have diarrhea with complications, such as pneumonia, sepsis, electrolyte abnormalities, severe malnutrition, or seizure or altered consciousness, are admitted to long stay wards for thorough clinical and laboratory assessments and treatment. These patients stay for an average of 5.5 days. Patients with very severe illnesses, such as severe respiratory distress, cyanosis, suspected septic shock, or convulsions, are admitted to the special care wards for more intensive care. The research review and the ethical review committees of the ICDDR,B approved the protocol. The patients received standard routine medical care, including the reduced osmality ORS; therefore, consent for an experimental protocol was not obtained.

**Inclusion and Exclusion Criteria**
All patients attending the Dhaka and Matlab hospitals with uncomplicated, acute watery diarrhea who were admitted to the short stay wards and who stayed for at least 8 hours for rehydration were eligible for the study. At the Dhaka hospital, patients with some or severe dehydration attending between 8:30 AM and 8:30 PM and all patients irrespective of their dehydration status attending beyond this time interval are usually admitted to the short stay ward. Patients without any sign of dehydration attending between 8:30 AM and 8:30 PM are referred to a clinic within the ICDDR,B premises run by a nongovernment organization. At the Matlab hospital, all patients irrespective of their dehydration status are admitted to the short stay ward.

Dehydration status of the patients was assessed by a senior nurse at the registration desk following the WHO guidelines modified for use in the ICDDR,B hospitals. Some dehydration was defined as the presence of at least 2 signs or symptoms (irritable or less active, sunken eyes, dry mucosa, thirst, reduced skin turgor) with at least 1 key sign (irritable or less active, thirst, or reduced skin turgor). Severe dehydration was defined as the presence of signs or symptoms of some dehydration with at least 1 key sign (lethargy or coma, unable to drink but not refusal, or uncountable or absent radial pulse). Patients with complications on admission (lethargy, altered consciousness, convulsion, or other chronic
illnesses) and those patients with associated severe illnesses (pneumonia, sepsis, meningitis, shigellosis, or typhoid fever) that required special care and multiple interventions were excluded from the study.

**Procedures**

All patients received the new reduced-osmolarity ORS, with the following salt concentrations: sodium, 75 mEq/L; chloride, 65 mEq/L; potassium, 20 mEq/L; and citrate, 290 mg/dL. The solutions for infants aged 6 months or younger used glucose (1351 mg/dL [75 mmol/L]) as the carbohydrate substrate, and the solutions administered to older children and adults used rice powder (40 g/L) as the carbohydrate source in accordance with the standard policy of the ICDDR, B. The osmolarity of the glucose solution was 245 mOsm/L, and the osmolarity of the rice ORS was 170 mOsm/L.

**Case Detection and Management**

Patients who developed seizures or altered consciousness during their hospitalization in the short stay ward were transferred to the long stay ward or the special care ward, where they were monitored at the 2 hospitals during the study period. Patients who were febrile to exclude meningitis, and a venous blood sample was sent for culture to exclude septicemia. A chest radiograph was performed to exclude pneumonia when clinically indicated. Stool cultures for *Shigella*, *Salmonella*, and *Vibrio* species were performed to look for common bacterial causes of diarrhea, although some patients had received antimicrobial drugs while being treated in the short stay ward because of a clinical diagnosis of cholera or shigellosis. Patients with severe hyponatremia (serum sodium, ≤120 mEq/L) were treated with 3% sodium chloride (12 mL/kg over a 4-hour period) along with restriction of plain water. Follow-up serum sodium estimations were performed if required, according to the patients’ response. Patients who were hypernatremic with diarrhea were treated using the study ORS but with provision for water ad lib. Patients suspected of having other infections, including sepsis, were treated with parenteral ampicillin plus gentamicin (infants aged ≤6 months) or ceftriaxone plus gentamicin (patients aged >2 months) for 7 days.

**Comparison Group**

Because this was not a controlled study, we reviewed the hospital records of all patients admitted to the long stay or special care wards of the Dhaka hospital in the previous year (December 1, 2001–November 30, 2002). Those patients initially admitted to the short stay ward who stayed for at least 8 hours but subsequently developed neurological symptoms (seizure or altered consciousness) and were transferred to the long stay or special care wards were included for comparison.

**Data Analysis**

All data were collected on case report forms, edited, entered into a personal computer, and analyzed on completion of the study using statistical software (SPSS version 10, SPSS Inc, Chicago, Ill). All episodes of seizure or altered consciousness were identified and recorded, and their association with abnormal levels of serum sodium or glucose was determined. Denominators were the number of children with diarrhea admitted to the short stay wards at the 2 hospitals during the study period, taken from hospital records. The main outcome measure of the study was the incidence of seizures or altered consciousness due to hyponatremia during hospitalization. Hospital records from the Dhaka hospital in the past year were also reviewed to allow comparison of the incidence of symptomatic hyponatremia in the current study period with that of the previous year using χ² test. Odds ratio was calculated to estimate the risk of symptomatic hyponatremia using the reduced osmolarity ORS. P<.05 was considered statistically significant.

**RESULTS**

In total, 53 280 patients with diarrhea were monitored at the 2 hospitals (43 700 at the Dhaka hospital and 9580 at the Matlab hospital) during the study period, with 22 536 children aged younger than 60 months. For the comparison period, 48 511 patients were admitted to the short stay ward. Proportionately more male children presented to both hospitals, which might reflect the health-seeking behavior of the Bangladeshi people with a male preference. The majority of children...
5 years or younger at the Dhaka hospital experienced some dehydration (59%); 12% had severe dehydration and 29% had no sign of dehydration. At the Matlab hospital, 66% of the children of the same age group were admitted with no sign of dehydration. Among older children and adults, most were admitted with either some dehydration (48% at Dhaka hospital and 53% at Matlab hospital) or severe dehydration (47% at Dhaka hospital and 27% at Matlab hospital). Most children younger than 3 years were brought to the hospital with a history of diarrhea and most older children and adults were admitted with either some dehydration or severe dehydration associated with hyponatremia, of whom 4 were adults.

During the study period, 24 children aged 3 years or younger experienced seizures or altered consciousness associated with hyponatremia (21 at the Dhaka hospital and 3 at the Matlab hospital). In the comparison period, 40 patients aged 3 years or younger were identified with symptoms of seizure or altered consciousness associated with hyponatremia.

The overall rate of symptomatic hyponatremia was 0.05% (21/43 700; 95% confidence interval [CI], 0.03%-0.07%) at the Dhaka hospital and 0.03% (3/9580; 95% CI, 0.01%-0.09%) at the Matlab hospital. The overall rate in the comparison period across all age groups was 0.10% (47/48 511; 95% CI, 0.07%-0.13%).

Statistical comparison of the incidence rate during the study period vs comparison periods revealed a statistically significant 50% lower incidence of symptomatic hyponatremia in the study period (p²=6.80; odds ratio, 0.50; 95% CI, 0.29-0.85; P=.009). Combining the data from the 2 hospitals, the rate was 0.12% (24/20 090; 95% CI, 0.08%-0.18%) for those children aged 3 years or younger; 0.19% (8/4156; 95% CI, 0.10%-0.38%) for those aged 6 months or younger; and 0.10% (16/19 934; 95% CI, 0.06%-0.16%) for those aged 7 to 36 months, following the introduction of the new formulation of ORS. Because patients presenting with severe dehydration are at greatest risk of developing symptomatic hyponatremia while being treated with reduced osmolarity ORS, a subgroup analysis excluding patients with no or some dehydration was performed. The incidence rate during the study period (combined data from Dhaka and Matlab hospitals) was 0.15% (24/16 077; 95% CI, 0.10%-0.22%).

In the 2 hospitals, 7 patients developed seizures or altered consciousness without hyponatremia (Table 3). In 3 patients, symptoms were associated

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Table 1. Distribution of Patients by Age, Sex, and Dehydration Status*

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Total No. of Patients</th>
<th>Dhaka Hospital (n = 43 700)</th>
<th>Matlab Hospital (n = 9580)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>≤6 mo</td>
<td>3415</td>
<td>2174 (64)</td>
<td>1241 (36)</td>
</tr>
<tr>
<td>7-36 mo</td>
<td>11 380</td>
<td>7141 (63)</td>
<td>4239 (37)</td>
</tr>
<tr>
<td>37-60 mo</td>
<td>1 818</td>
<td>1098 (60)</td>
<td>720 (40)</td>
</tr>
<tr>
<td>1-2 y</td>
<td>4882</td>
<td>2923 (60)</td>
<td>1953 (30)</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>22 205</td>
<td>12 657 (57)</td>
<td>9548 (43)</td>
</tr>
</tbody>
</table>

*Some dehydration status is defined as the presence of at least 2 signs or symptoms (irritable or less active, sunken eyes, dry mucosa, thirst, reduced skin turgor) with at least 1 key sign (irritable or less active, thirst, or reduced skin turgor). Severe dehydration status is defined as the presence of signs or symptoms of some dehydration with at least 1 key sign (lethargy or coma, unable to drink but not refusal, or uncountable or absent radial pulse).

Table 2. Duration of Diarrhea Before Admission by Age

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Total No. of Patients</th>
<th>Dhaka Hospital (n = 43 700)</th>
<th>Matlab Hospital (n = 9580)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤1</td>
<td>2-7</td>
<td>&gt;7</td>
</tr>
<tr>
<td>≤6 mo</td>
<td>3415</td>
<td>717 (21)</td>
<td>2391 (70)</td>
</tr>
<tr>
<td>7-36 mo</td>
<td>11 380</td>
<td>3498 (31)</td>
<td>7253 (64)</td>
</tr>
<tr>
<td>37-60 mo</td>
<td>1818</td>
<td>989 (54)</td>
<td>798 (44)</td>
</tr>
<tr>
<td>1-2 y</td>
<td>4882</td>
<td>3027 (62)</td>
<td>1756 (36)</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>22 205</td>
<td>14 210 (64)</td>
<td>7551 (34)</td>
</tr>
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with hypernatremia. In the comparison period, 7 patients had seizures or altered consciousness without hyponatremia, and 1 of them had borderline hypernatremia (serum sodium, 151.3 mEq/L). One moderately malnourished 8-month-old female died during the study period due to culture-proven shigellosis with severe pneumonia, sepsis, and hypernatremia (serum sodium, 118.5 mEq/L) 3 days after admission.

**COMMENT**

The results of our large, phase 4 clinical surveillance study demonstrate that the occurrence of symptomatic hyponatremia in older children and adults with diarrhea who are treated with the reduced osmolarity ORS formulation recently recommended by WHO and UNICEF is extremely rare. None of more than 30,000 older children or adults developed symptomatic hypernatremia. Among younger patients (≤3 years), a few developed neurological symptoms associated with hyponatremia while being treated with the new ORS formulation. However, the rate of symptomatic hypernatremia was not higher but rather lower than the rate of symptomatic hypernatremia during the previous year when the older ORS formulation containing a higher amount of sodium was used. Even when patients with diarrhea with no or some dehydration who were less likely to develop symptomatic hypernatremia while being treated with reduced osmolarity ORS were excluded, the incidence rate was still very low.

At these hospitals, fecal specimens are cultured from every 50th patient (a 2% systematic sample) to characterize the etiological agents causing diarrhea. This surveillance demonstrates that approximately 20% of the patients have culture-documented cholera, and the rate has remained reasonably constant over the years. Although fecal cultures were not performed on all the patients in our study, we can assume that cholera was common. In severe cholera, the stool contains high concentrations of sodium; therefore, there was a concern that patients with cholera, especially adults whose stool sodium concentration is much higher than that of children, would be at particularly high risk of hypernatremia when treated with an ORS containing 75 mEq/L of sodium. Although we did not measure serum sodium in our patients, it is reassuring that symptomatic hypernatremia did not occur in older children and adults. Of 21 patients aged 3 years or younger at the Dhaka hospital who had neurological symptoms, 5 (24%) were diagnosed to have

<table>
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<th>Table 3. Characteristics of Patients Who Developed Seizure or Altered Consciousness While Being Treated With ORS*</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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<td>---</td>
</tr>
<tr>
<td>≤6 mo</td>
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<tr>
<td>7-36 mo</td>
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<tr>
<td>37-60 mo</td>
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<td>6-15 y</td>
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<tr>
<td>&gt;15 y</td>
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<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Neurological symptoms</strong></td>
</tr>
<tr>
<td>Seizure</td>
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<tr>
<td>Altered consciousness</td>
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<tr>
<td><strong>Timing of development of symptoms after admission in short stay ward, h</strong></td>
</tr>
<tr>
<td>8-24</td>
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<tr>
<td>25-48</td>
</tr>
<tr>
<td>&gt;48</td>
</tr>
<tr>
<td><strong>Serum sodium, mEq/L</strong></td>
</tr>
<tr>
<td>&lt;115</td>
</tr>
<tr>
<td>115-120</td>
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<tr>
<td>121-125</td>
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<tr>
<td>126-129</td>
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<tr>
<td>130-150</td>
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<tr>
<td>&gt;150</td>
</tr>
<tr>
<td><strong>Presentation/clinical diagnoses</strong></td>
</tr>
<tr>
<td>AWD</td>
</tr>
<tr>
<td>AWD + pneumonia</td>
</tr>
<tr>
<td>AWD + fever</td>
</tr>
<tr>
<td>AWD + sepsis</td>
</tr>
<tr>
<td>Dysentery + pneumonia + sepsis</td>
</tr>
<tr>
<td>AWD + acute renal failure</td>
</tr>
<tr>
<td>AWD + hepatic encephalopathy</td>
</tr>
<tr>
<td><strong>Bacterial etiology of diarrhea</strong></td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td>Shigella species</td>
</tr>
<tr>
<td>Shigella + nontyphoidal Salmonella</td>
</tr>
<tr>
<td><em>Salmonella typhi</em></td>
</tr>
<tr>
<td><strong>Associated findings</strong></td>
</tr>
<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Hypocalcemia</td>
</tr>
</tbody>
</table>

Abbreviations: AWD, acute watery diarrhea; ORS, oral rehydration solution.

*Reduced osmolarity ORS (sodium, 75 mEq/L) was used during the study periods at the Dhaka and Matlab hospitals and the old formulation of ORS (sodium, 90 mEq/L) was used at the Dhaka hospital in the comparison study period. The Dhaka hospital study period was from December 1, 2002, to November 30, 2003; the Matlab hospital study period was from February 2, 2003, to January 31, 2004; and the Dhaka hospital comparison study period was from December 1, 2001, to November 30, 2002.
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cholera. Similarly, in the corresponding months of the previous year, 24 (25%) of 47 patients diagnosed with neurological symptoms and hyponatremia had cholera. In a previous trial that used an ORS containing 67 mEq of sodium, moderate hyponatremia (serum sodium, <125 mEq/L) was observed in 8.8% of the patients. An increased number of patients with transient hyponatremia was also reported in another study in which adult patients with cholera were treated with reduced osmolarity ORS containing 75 mEq/L of sodium. However, transient mild hyponatremia, which may also occur with old ORS, should be corrected when a normal diet is resumed. A similar view was expressed by the investigators of ORS trials, although concerns and counter arguments continue. Stool sodium excretion in children with acute watery diarrhea caused by organisms other than Vibrio cholerae generally does not exceed the concentrations present in the new ORS formulation, and younger children mostly have noncholera diarrhea, and thus these groups are of less concern.

We used rice-based ORS for patients older than 6 months instead of the standard glucose-based ORS recommended by the WHO. Rice-based ORS has been proven to be beneficial in cholera because it is associated with significantly less purging, and it is equally effective in diarrhea due to other causes. Because patients treated at our hospitals frequently have cholera, the policy of the ICDDR, B hospitals is to use rice-based ORS for children older than 6 months and for adults with diarrhea. The concentrations of the salts (sodium, potassium) and bases are the same in the rice-based and glucose-based formulations and, therefore, we think that the results obtained in our study can be safely extrapolated to glucose-based reduced osmolarity ORS.

Other common causes of seizure or altered consciousness in patients admitted to the special care wards are severe infections, such as shigellosis, salmonellosis, sepsis, meningitis, and severe pneumonia. Hypernatremia or hypoglycemia must also be considered in children with diarrhea and seizures, especially in younger children. In our study, convulsions due to hypoglycemia were rare, perhaps because of the use of ORS and the early feeding. Benign convulsions in infants and children with mild gastroenteritis due to rotavirus have also been reported.

Although this was a 1-year study covering all seasons with a large sample size, there are some limitations. There was no concurrent control for comparison. Although we have compared the results to the previous year’s data, there remains the possibility of bias. No phase 4 clinical trial was performed with the older ORS and thus direct comparison was not possible. This was a hospital-based study and may not be representative of the field situation. However, children and adults treated in the community are likely to have milder illness compared with those presenting to a hospital. Therefore, it is likely that hyponatremia will be even less common with the use of reduced osmolarity ORS in the community.

Besides hyponatremia, seizures in patients with diarrhea, especially in younger children, may occur with other associated conditions (hypoglycemia, hypernatremia, hypocalcemia, hypomagnesemia, shigellosis, sepsis, pneumonia, meningitis, high fever), and it is difficult to determine the actual cause of seizure when 2 or 3 conditions overlap. In addition to hyponatremia, 7 children developing seizures in our study had other conditions: 1 had shigellosis with clinical sepsis and pneumonia, 1 had shigellosis and pneumonia, 1 had shigellosis and hypoglycemia, 1 had pneumonia and hypocalcemia, 2 had pneumonia and clinical sepsis, and 1 had hypocalcemia. All were categorized as having seizures from hyponatremia rather than the other conditions, and all presented with watery diarrhea. Younger children who experienced enteric infection with Shigella species other than S. dysenteriae type 1 often present with watery diarrhea, which delays antimicrobial treatment and the benefits of early specific therapy.

Based on the experience from our study and other trials, we conclude that diarrheal diseases are most often uncomplicated and simple to treat but a few patients may still present with or develop complications during treatment, irrespective of fluid therapy and whether it is iso-osmolar or hypo-osmolar. Therefore, centers treating infectious diarrheal diseases should be vigilant about the development of such complications and should follow a protoclated treatment strategy to handle them. The formulation of reduced osmolarity ORS recently recommended by WHO and UNICEF is safe and can be used in the treatment of all patients with diarrhea, irrespective of their age and the cause of diarrhea.

Author Contributions: Dr Alam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Alam, Faruque, Gyr, Salam, Sack.

Acquisition of data: Alam, Yunus, Faruque, Sattar, Parvin, Ahmed, Salam, Sack.

Analysis and interpretation of data: Alam, Yunus, Faruque, Gyr, Sattar, Parvin, Ahmed, Salam, Sack.

Drafting of the manuscript: Alam, Yunus, Gyr, Sattar, Parvin, Ahmed, Salam, Sack.

Critical revision of the manuscript for important intellectual content: Alam, Yunus, Faruque, Gyr, Salam, Sack.

Statistical analysis: Alam, Faruque, Gyr, Sattar, Parvin, Ahmed, Salam.

Obtained funding: Alam, Salam, Sack.

Administrative, technical, or material support: Alam, Yunus, Faruque, Gyr, Sattar, Parvin, Ahmed, Salam, Sack.

Study supervision: Alam, Yunus, Faruque, Gyr, Sattar, Parvin, Ahmed, Salam, Sack.

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2. Victoria CG, Bryce J, Fontaine O, Monash R. Re-ducing deaths from diarrhoea through oral rehydra-
tion therapy. Bull World Health Organ. 2000;78:1246-
1255.
7. Report of an ESPGAN Working Group. Recommenda-
tions for composition of oral rehydration solu-
tions for the children of Europe. J Pediatr Gastro-
8. Thilainayagam AV, Hunt JB, Farthing MJ. Enhanc-
9. Farthing MJ. Disease-related animal models for op-
10. Hunt JB, Elliot EJ, Farthing MJ. Efficacy of a stan-
11. Rolston DD, Zinzuaudia SN, Mathan VI. Evalua-
13. Hunt JB, Thilainayagam AV, Carnaby S, Fair-
ganization oral rehydration with a reduced osmolar-
16. Alam NH, Mazumder RN, Fuchs GJ; CHOICE Study Group. Efficacy and safety of oral rehydration solu-
17. CHOICE Study Group. Multicentre, random-
ized, double blind clinical trial to evaluate the effi-
cacy and safety of a reduced osmolarity oral rehydra-
19. Faruque ASG, Malahanabis D, Hamadani JD, Zet-
20. Murphy C, Hahn S, Volmink J. Reduced osmo-
21. World Health Organization. The Treatment of Di-
22. Chen LC, Huq E, D’Souza S. Sex bias in the fam-
25. Duggan C, Fontaine O, Pierce NF, et al. Scien-
tific rationale for a change in the composition of oral rehydration solution. JAMA. 2004;291:2628-2631.
26. Nalin DR, Hirschhorn N, Greenough W III, Fuchs GJ, Cash RA. Clinical concerns about reduced osmo-
larity oral rehydration solution. JAMA. 2004;291:2632-
2635.
28. Raizada N, Bhata RC, Jain BK, Singh H. Stool elec-
30. Fontaine O, Gore SM, Pierce NF. Rice-based oral rehydration solution for treating diarrhoea. Coch-
31. Khan WA, Dhar U, Salam MA, Griffiths JK, Rand W, Bennish ML. Central nervous system manifesta-
tions of childhood shigellosis: prevalence, risk fac-
32. Mitra AK, Khan MR, Alam AN. Complications and outcome of disease in patients admitted to the inten-
sive care unit of a diarrhoeal diseases hospital in Bangladesh. Trans R Soc Trop Med Hyg. 1991;85:685-
687.
36. Bennish ML, Azad AK, Rahman O, Phillips RE. Hy-
poglycemia during diarrhea in childhood: preva-
38. Wang YC, Hung KL. Benign seizures associated with mild diarrhea: clinical analysis of 20 cases. Zhon-
ghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1993;34:451-457.