Stability Study of Oral Rehydration Salt (ORS) in Pakistan

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Abstract: Acute diarrhea is one of the leading causes of mortality among infants and young children in developing countries like Pakistan, caused by dehydration. The United Nations Children’s Fund (UNICEF) is active in providing large quantities of oral rehydration salts (ORS) for the treatment of dehydration. So, there is a serious need of conducting the real time and accelerated stability studies for ORS in Pakistan because of loop holes in the maintenance of supply. Stability study of 43 Lots out of 554 lots of ORS labeled ORS-1 to ORS-43 manufactured at National Institute of health (NIH), was carried out at different interval of time to analyze whether the ORS is stable and effective up to its shelf life of 24 months and beyond its shelf life i.e. 30 months 36 months and 42 months. It is keenly observed that storage of ORS at proper temperature is very important for its stable formulation and long-term usage.

1. Introduction

Acute diarrheal are one of the leading cause of mortality among infants and young children in developing countries like Pakistan, caused by dehydration. Dehydration from diarrhea can be prevented by giving extra fluids at home, or it can be treated simply, effectively and cheaply in all age groups and in all but the most severe cases by giving patients by mouth an adequate glucose-electrolyte solution. Oral rehydration therapy (ORT), combined with guidance on appropriate feeding practices, is the main strategy recommended by the WHO Department of Child and Adolescent Health and Development (CAH) to achieve a reduction in diarrhea-related mortality and malnutrition in children.

A new formula for oral rehydration salts (ORS), has been released by the World Health Organization. The new formula ORS, a sodium and glucose solution, is widely used to treat children with acute diarrhea. Since WHO adopted ORS in 1978 as its primary tool to fight diarrhea, the mortality rate for children suffering from acute diarrhoea has fallen from 5 million to 1.3 million deaths annually.

The new improved formula is the result of extensive research sponsored by WHO’s Department of Child and Adolescent Health and Development and supported by the United States Agency for International Development (USAID). The latest study was conducted in five developing countries among children from one month to two years old with acute diarrhea and dehydration.

The study’s findings suggest that using the low-sodium, low-glucose ORS formulation reduces the need for intravenous fluids by 33 percent. The effect of this reduction could result in fewer children requiring hospitalization, fewer secondary infections, a diminished need to handle blood with its potentially dangerous consequences, and lower health care costs.

For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose-based oral rehydration salts to prevent or treat dehydration from diarrhoea irrespective of the cause or age group affected. This product, which provides a solution containing 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l, has proven effective and without apparent adverse effects in worldwide use. It has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during the period.

For the past 20 years, numerous studies have been undertaken to develop an “improved” ORS. The goal was a product that would be at least as safe and effective as standard ORS 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 consisted in reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution’s glucose and salt (NaCl) concentrations.

Studies to evaluate this approach were reviewed at a consultative technical meeting held in New York (USA) in July 2001, and technical recommendations were made to WHO and UNICEF on the efficacy and safety of reduced osmolarity ORS in children with acute non-cholera diarrhoea, and in adults and children with cholera.

In developing countries like Pakistan, there is a need of conducting the real time and accelerated stability studies for ORS because of loop holes in the maintenance of supply.

2. Material and Equipment:

2.1. Material /Chemicals

Sample of Oral Rehydration Salt (ORS).

Distilled Water

2.2. Equipment/Glassware

Beaker, 100 ml.

Pipettes, 01ml, 05ml, 10ml.

Volumetric flask (1000 ml, 500ml, 100ml)

Analytical Balance

Flame photometer

2.3. Procedure

“Solution A”: Solution “A” is prepared by dissolving 8 grams Oral Rehydration Salt (ORS) accurately weighed in sufficient water to produce 500ml.

Test solution: 3ml of solution “A” is diluted up to 500ml with water.

Standard solution, “100%”: Standard solution is prepared by dissolving sodium chloride 508.4mg sodium chloride, previously dried to constant weight; in water to make 1000ml. (0.2mg Na⁺/ml). For the preparation of reference solution, 2ml of the standard solution is diluted with water to make 50ml.

Standard solution “110%”: Standard solution is prepared by dissolving sodium chloride 559.2 mg, previously dried to constant weight, in water to make 1000 ml. (0.18 mg Na⁺/ml). For the preparation of reference solution, 2ml of the standard solution is diluted with water to make 50ml.

Select filter of Flame photometer of wavelength 589nm for the determination of Sodium.

Aspirate water as a blank solution and calibrate the zero.

Aspirate the reference solution and adjust the sensitivity for correct reading.

Recheck the zero, aspirate the reference solutions turn by turn and record the reading of r₁₀₀, r₉₀, r₁₁₀

Aspirate the test solution and record the result “t”. Calculate the Sodium using formula

\[ t \times 74.1/r₁₀₀ = \text{mmol Na}^+ /\text{dose. allowed.} \]

3. Results and Discussion

These studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhoea is improved by reducing its sodium concentration to 75 mEq/l, its glucose concentration to 75 mmol/l, and its total osmolarity to 245 mOsm/l. The need for unscheduled supplemental IV therapy in children given this solution was reduced by 33%. In a combined analysis of this study and studies with other reduced osmolarity ORS solutions (osmolarity 210-268 mOsm/l, sodium 50-75 mEq/l) stool output was also reduced by about 20% and the incidence of vomiting by about 30%. The 245 mOsm/l solutions also appeared to be as safe and at least as effective as standard ORS for use in children with cholera.

<table>
<thead>
<tr>
<th>Reduced osmolarity</th>
<th>grams/litre</th>
<th>Reduced osmolarity</th>
<th>mmol/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORS</td>
<td></td>
<td>ORS</td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>2.6</td>
<td>Sodium</td>
<td>75</td>
</tr>
<tr>
<td>Glucose, anhydrous</td>
<td>13.5</td>
<td>Chloride</td>
<td>65</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.5</td>
<td>Glucose</td>
<td>75</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>Anhydrous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisodiumcitrate dehydrate</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Osmolarity</td>
<td>245</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Charts below represent the analytical data for the stability of ORS to its shelf life of 24 months and beyond its shelf life i.e. 30 months, 36 months, and 42 months. Chart 1 to chart 5 represents the analytical data for the stability of Total osmolarity of ORS to its shelf life of 24 months and beyond its shelf life i.e. 30 months, 36 months, and 42 months. Chart 6 to chart 10 represents the analytical data for the stability of pH of ORS to its shelf life of 24 months and beyond its shelf life i.e. 30 months, 36 months, and 42 months.
For more than 25 years WHO and UNICEF have recommended a single formulation of glucose-based Oral Rehydration Salts (ORS) to treat or prevent dehydration from diarrhoea of any aetiology, including cholera, and in individuals of any age.

This product, which makes a solution that contains 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l, has been used worldwide and has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during this period (2). It has been well established, however, that ORS solution does not reduce stool output or duration of diarrhoea (3). There has been concern that this may limit its acceptance by mothers and health workers, who want a treatment that causes diarrhoea to stop. There has also been concern that the solution, which is slightly hyperosmolar when compared with plasma, may risk hypernatremia or an osmotically driven increase in stool output, especially in infants and young children (4-6). For this reason, pediatricians in some developed countries recommend that ORS contain about 60 mEq/l sodium and have a total osmolarity of 250 mOsm/lS.

During the past 20 years, numerous studies have been undertaken to develop an “improved” ORS that would be optimally safe and effective for treating or preventing dehydration in all types of diarrhoea, and would also cause reduced stool output or have other clinical benefits when compared with standard ORS. Two approaches have been used: (i) modifying the amount and type of organic carrier(s) used in ORS to promote intestinal absorption of salt and water (this has included replacing glucose with complex carbohydrates, i.e. maltodextrins or cooked rice powder, or certain amino acids, or combining an amino acid with glucose), and (ii) reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption (this was done either by replacing glucose with a complex carbohydrate or by reducing the concentration of glucose and salt in the solution). At a meeting in Dhaka, Bangladesh, in 1994, studies that evaluated these two approaches were reviewed. Conclusions reached at that meeting were:

- None of the tested formulations containing an amino acid or maltodextrin was considered sufficiently effective or practical to replace standard ORS (9).
- Rice-based ORS significantly reduces stool output and duration of diarrhoea when compared to standard ORS for adults and children with cholera, and may be used to treat such patients wherever its preparation is convenient (10), and
- Rice-based ORS is not superior to standard glucose-based ORS in the treatment of children with acute non-cholera diarrhoea, especially when food is given shortly after rehydration, as is recommended to prevent malnutrition [10-12].
Concerning ORS formulations in which osmolarity was reduced by lowering the content of glucose and salt to 75-90 mmol/l and 60-75 mEq/l respectively (total osmolarity of 225-245 mOsm/l), it was concluded that:

Reduced osmolarity ORS significantly reduces stool output and duration of diarrhea when compared to treatment with standard ORS for children with acute non-cholera diarrhea, but there were insufficient data to reach firm conclusions with regard to the possible risks and benefits of reduced osmolarity ORS for treatment of patients with cholera, especially adults. Moreover, the compositions of the reduced osmolarity ORS solutions differed with regard to concentrations of sodium and glucose, and in total osmolarity, and it was not possible to recommend one formulation as being superior to the others.

It was recommended that additional studies be done in adults with cholera and in children with acute non-cholera diarrhea comparing standard ORS to a single reduced osmolarity ORS solution containing 75 mmol/l of glucose and 75 mEq/l of sodium, and a total osmolarity of 245 mOsm/l (Table 1). This formula was selected to provide a sodium concentration only modestly less than that in standard ORS, which was considered important for treatment of adults with cholera in whom sodium losses are greatest, and to provide glucose in a molar concentration equal to that of sodium, which is essential to facilitate sodium absorption. These studies were conducted from 1995 to 1998 in six countries (Bangladesh, Brazil, India, Indonesia, Peru and Viet Nam), and were supported by the Department of Child and Adolescent Health and Development of WHO (Geneva), the Applied Research of Child Health (ARCH) project (Boston, USA), USAID and UNICEF. The objectives of the present meeting were to review the results of both the previous and the new studies, and to provide technical recommendations to WHO and UNICEF on the safety and efficacy of reduced osmolarity ORS in adults and children with cholera, and in children with acute non-cholera diarrhea.

Results of a study by Alam et al comparing the efficacy and safety of reduced osmolarity ORS (RED OSM ORS) and standard ORS (WHO ORS) in adults with cholera were reviewed. The study enrolled 300 patients who presented with signs of severe dehydration (147 treated with reduced osmolarity ORS and 153 treated with standard ORS). There were no differences in: stool output during the first 24 hours, total stool output, duration of diarrhea, need for unscheduled IV therapy, or the incidence of treatment failure when comparing patients given reduced osmolarity ORS with those receiving standard ORS. Patients who received reduced osmolarity ORS did have an increased risk of hyponatremia after 24 hours of treatment, defined as a serum sodium concentration <130 mEq/l (29 patients treated with reduced osmolarity ORS developed hyponatremia versus only 16 in the group treated with standard ORS; OR=2.1, 95% CI 1.1 to 4.1). However, the proportion of patients with serum sodium < 125 mEq/l 24 hours after initiation of treatment was similar in the two groups. No patient had symptoms due to hyponatremia. Additional data, not included in the published report, were also referred to. Among 35 patients who underwent sodium balance studies, mean sodium balance was negative in both groups and the negative balance was greater in the reduced osmolarity ORS group. However, there was wide variability in balance outcomes and this difference did not achieve statistical significance. Results of this study were analyzed together with those of two earlier studies (14-15) that compared the efficacy and safety of reduced osmolarity ORS to that of standard ORS in adults with cholera. The combined analysis showed a minimal, and statistically insignificant, mean reduction of 0.5 ml/kg (95% CI: −14.6 to 15.6) in stool output during the first 24 hours among patients given reduced osmolarity ORS when compared to those receiving standard ORS. A small, but statistically significant reduction in mean serum sodium of 1.3 mEq/l (95% CI: 0.3 to 2.3) was observed at 24-hours in patients treated with reduced osmolarity ORS when compared to those given standard ORS (Table 2). In these studies, no patient who developed hyponatremia became symptomatic.

Table 2: Comparison of serum sodium values at 24 hours in adult cholera patients treated with reduced osmolarity ORS or standard ORS [2].

<table>
<thead>
<tr>
<th>Author</th>
<th>No. analyzed</th>
<th>Osmolarity of ORS</th>
<th>Serum sodium at 24 hours</th>
<th>Study weight in pooled analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alam et al.</td>
<td>29/34</td>
<td>RED OSM ORS</td>
<td>Mean sodium with WH ORS: mEq/l (sd)</td>
<td>Meana reduction in sodium with RED OSM ORS: mEq/l (sd)</td>
</tr>
<tr>
<td>Faruque et al.</td>
<td>249</td>
<td>137 (4.4)</td>
<td>2.4 (1.8)</td>
<td>0.12 8</td>
</tr>
<tr>
<td>Pulungsih</td>
<td>67/64</td>
<td>141</td>
<td>0.7</td>
<td>0.10</td>
</tr>
</tbody>
</table>
et al. (14) & (9.9) & (2.2) & 5 \\
Alam et al. (12) & 153/1 & 245 & 135 & (4.3) & 1.2 & (0.3) & 0.76 & 7 \\

$\text{se}^2$ = variance of the mean \\
$\text{sd}$ = standard deviation \\
Pooled analysis: Estimated mean serum Na at 24 hours for patients given standard WHO ORS: 136 mEq/l \\
Mean reduction in serum sodium for patients given reduced osmolarity ORS solutions: 1.3 mEq/l; 95% CI: 0.3 to 2.3 \\

4. Conclusion 

It was concluded that for adults with cholera, a reduced osmolarity ORS solution with 75 mEq/l of sodium and 75 mmol/l of glucose is as effective as standard WHO/UNICEF ORS solution. Nevertheless, some concern remained about the possible risk of symptomatic hyponatraemia with this solution. This concern was not considered sufficient to prevent the use of this solution to treat adults with cholera. It was agreed, however, that, to gain additional clinical data on the safety of reduced osmolarity ORS, the incidence of biochemical and symptomatic hyponatraemia should be monitored when this solution is first introduced for routine use. Because seizures are rare in adults with cholera, an increase in the incidence of this symptom should be easily recognized.

So, the recommended Optimal storage conditions are 20°C and 60% relative humidity. This stability study is conducted on stored packets of ORS stored at room temperature <25o C. Results of all parameters tested for ORS conclude that it is quiet stable formulation and maintenance of proper temperature i.e. <25o C is recommended for delivery of ORS in countries with high but ambient temperature.

5. Acknowledgements 

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6. References 


[2] Parameters for the control of Diarrhoeal Diseases. The selection of fluids and food for home therapy to prevent dehydration from diarrhoea: Guidelines for developing a national policy. WHO/CDD/93.44 


