



Child Health Research Project

Synopsis: Reformulating Oral Rehydration Salts: A Treatment for Children with Diarrhea

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Summary: In 1975, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) agreed to promote a single, orally administered solution of oral rehydration salts (ORS) to prevent dehydration caused by diarrhea. However the ideal composition of this solution has been a point of controversy for many years. The studies discussed in this Synopsis examine the best possible composition for an oral rehydration salts (ORS) solution, especially with regard to the sodium and glucose concentrations and the overall solution concentration or osmolarity. The studies were conducted from 1995 to 1998 in Bangladesh, Brazil, India, Indonesia, Peru, and Viet Nam. They compared standard ORS to a single reduced osmolarity ORS containing 75 mmol/L of glucose and 75 mEq/L of sodium, and a total osmolarity of 245 mOsm/L in children with both cholera and non-cholera diarrhea as well as adults with cholera. It was found that the efficacy of glucose-based ORS for treatment of children with acute non-cholera diarrhea is improved by reducing sodium to 60–75 mEq/L, glucose to 75–90 mmol/L, and a total osmolarity to 215 to 260 mOsm/L. Solutions containing the same composition also appeared to be safe and effective for use in children with cholera. The reduced osmolarity ORS solution proved to be as effective in adults with cholera. Overall a total of 14,000 deaths per million episodes of diarrhea would be avoided with the reduced osmolarity ORS solution, by reducing the number of treatment failures. This would result in a cost savings of \$500 per death averted, or \$7.1 million per million episodes. The findings displayed the following benefits to changing the sodium and glucose concentrations of the ORS solution: 1) reduced the need for intravenous (IV) therapy, which reduced the cost of treatment risk, 2) reduced treatment failure which led to reduced risk of death. These studies emphasize the importance of issuing a reformulation of the standard ORS solution which will result in a decrease in deaths among children as well as achieve long-term economic benefits to health programs in developing countries.

A Simple Solution, Made Better

Each year diarrheal diseases cause an estimated 1.5 million deaths in children less than five years of age¹. This accounts for 12 percent of all infant and child deaths in developing countries. In a world where high-tech medicine has taken center stage, it is indeed humbling to see how a simple recipe of basic ingredients can dramatically reduce these preventable deaths². Even more astounding is to then realize that, as a result of research spanning more than 25 years, the solution has been improved from its original formula and is being recommended worldwide by the World Health Organization (WHO).

Until now, the widely distributed ORS solution, formulated by WHO and UNICEF, contained 90 mmol/L of sodium; 111 mmol/L of glucose; and had an overall concentration or osmolarity of 311 mmol/L¹. This ORS solution soon proved effective in treating dehydration associated with all types of diarrheal diseases including cholera in patients of all ages, but did not reduce stool

The solution: *Oral Rehydration Salts (ORS).*

The ingredients: *a mixture of glucose (sugar), sodium chloride (table salt), potassium chloride, and tri-sodium citrate. When mixed with drinking water and consumed, it replaces vital fluids lost as a result of diarrhea. Since its adoption almost three decades ago and its spread in developing countries, ORS has been responsible for saving millions of lives.*

output and vomiting during the rehydration phase³. This sometimes caused parents and hospital staff to discontinue treatment with ORS solution before rehydration was completed, thereby reducing treatment efficacy.

However, based on recent research findings emphasizing the benefits of issuing a reformulation of the standard ORS solution, WHO has issued a recommendation of a new, “improved” ORS solution, which is lower in sodium and glucose concentrations. The new ORS solution reduces the need for intravenous (IV) therapy, which reduces the cost of treatment risk, thus leading to long-term economic benefits to health programs in developing countries.

The Reformulation

The ideal composition of the oral rehydration solution has been a point of controversy for many years, especially with regard to the sodium and glucose concentrations and the overall solution concentration or osmolarity. The American Academy of Pediatrics and the European Society of Pediatric Gastroenterology and Nutrition recommended

the use of solutions containing significantly lower salt and total osmolarity than present in the solution that until now has been currently distributed worldwide^{4,5,6}. This reflected their concern that blood-sodium levels may rise too high (a condition known as hypernatremia) when solutions with high salt and high total osmolarity are given to well-nourished children. On the other side of the debate, practitioners in low-income settings have felt that a higher sodium content, as in the current ORS solution, was needed to replace the higher losses of sodium in cholera.

A number of studies were undertaken, which evaluated two approaches in developing an “improved” ORS solution that would be optimally safe and effective for treating or preventing dehydration in all types of diarrhea, and would cause reduced stool output in comparison with the standard ORS solution. The following approaches were taken: 1) modifying the amount and type of organic carrier used in ORS to promote intestinal absorption of salt and water, and 2) reducing the osmolarity of ORS to avoid possible adverse effects of hypertonicity on net fluid absorption. The first approach did not

Table 1. Composition of standard and reduced osmolarity ORS solutions**

	Standard ORS solution (mEq or mmol/l)	Reduced Osmolarity ORS solutions		
		(mEq or mmol/l)	(mEq or mmol/l)	(mEq or mmol/l)
Glucose	111	111	75 – 90	75
Sodium	90	50	60 – 70	75
Chloride	80	40	60 – 70	65
Potassium	20	20	20	20
Citrate	10	30*	10	10
Osmolarity	311	251	210 -260	245

*30 mmol/l of bicarbonate instead of 10 mmol/l of citrate

**Other reduced osmolarity ORS formulations include ORS in which glucose was replaced by maltodextrin (20) or sucrose (24).

Table 2: Summary of the results of the published meta-analysis of all randomized clinical trials comparing reduced osmolarity ORS solution with standard ORS solution in children with acute non-cholera diarrhea⁹.

	Pooled standardized mean difference (log scale) in children receiving RED. OSM ORS when compared to those receiving WHO ORS (95% CI)	Odds ratio for children receiving RED. OSM ORS when compared to those receiving WHO ORS: (95% CI)
Unscheduled IV therapy	–	0.61 (0.47 to 0.81)*
Stool output	0.214 (-0.305 to -0.123)*	–
Vomiting	–	0.71 (0.55 to 0.92)*
Hyponatremia	–	1.45 (0.93 to 2.26)
*p<0.05		

demonstrate a formulation that was both more effective and practical. After reviewing the studies that evaluated these two approaches at a meeting in Dhaka, Bangladesh in 1994⁷, it was recommended that additional studies be done in children with acute non-cholera diarrhea. These studies compared standard ORS to a single reduced osmolarity ORS (Table 1) containing 75 mmol/L of glucose and 75 mEq/L of sodium, and a total osmolarity of 245 mOsm/L. The reduced osmolarity ORS showed benefits over the standard ORS in a later trial conducted in Egypt⁸.

The additional studies were conducted from 1995 to 1998 in six countries (Bangladesh, Brazil, India, Indonesia, Peru, and Viet Nam). The studies, supported by the USAID's Child Health Research Project (CHR), were conducted by the WHO's Department of Child and Adolescent Health and Development of (Geneva), the Applied Research of Child Health (ARCH) project (Boston, USA), Johns Hopkins Family Health and Child Survival, and UNICEF. The following summaries outline the results and conclusions of these studies.

Reduced Osmolarity ORS in Children

Children with non-cholera diarrhea

A meta-analysis of all studies

A meta-analysis of trials of reduced osmolarity ORS solution was conducted⁹. The meta-analysis included all randomized trials in which a reduced osmolarity ORS containing glucose, maltodextrin or sucrose was used (total osmolarity 210–268 mOsm/l). Results of the analysis are as follows (Table 2): i) Use of a reduced osmolarity ORS solution was associated with a significant reduction (about 35%) in the need for unscheduled IV fluids, usually given during ORS treatment to maintain hydration after the patient is initially rehydrated. ii) In each of the 11 studies, except the one using maltodextrin, there was a trend toward reduced stool output in patients given reduced osmolarity ORS solution and in the pooled analysis this reduction (about 20%) was statistically significant. iii) There was a significant reduction (about 30%) in the incidence of vomiting in children given reduced osmolarity ORS solution. iv) And the incidence of hyponatremia (serum sodium <130mEq/l at 24 hours) was greater among children given reduced osmolarity ORS solution.

Multicentre trial of 75 mEq sodium, 75 mmol glucose ORS

A recent multicentre study evaluated the efficacy and safety of a reduced osmolarity ORS solution among children¹⁰. This study is included in the meta-analysis described above. It was conducted in 5 countries and enrolled 675 children aged 1 to 24 months (341 received reduced osmolarity ORS solution and 334 received standard ORS solution). In contrast to the meta-analysis summarized above, this study did not show any difference in stool output or vomiting between the two treatment groups, yet there was a significant reduction of about 33% in the use of unscheduled IV fluids in those who received reduced osmolarity ORS solution (34 children treated with reduced osmolarity ORS solution required unscheduled IV therapy versus 50 children in the group treated with standard ORS). The incidence of hyponatremia was 11% in the reduced osmolarity ORS solution group and 9% in the standard ORS group (37 children treated with reduced osmolarity ORS developed hyponatremia versus 29 in the group treated with standard ORS solution).

Re-analysis of ORS efficacy stratified for sodium content

A re-analysis of all studies was conducted, stratifying them according to the sodium content of the reduced osmolarity ORS solution. Results show that ORS solutions with sodium concentrations of 60–70 mEq/l and ORS solutions with a sodium concentration of 75 mEq/l are both more effective than standard ORS with regard to need for unscheduled IV therapy and occurrence of vomiting. They also showed that the incidence of hyponatremia, while not significantly higher than for the standard ORS solution, could be up to twice that seen with standard ORS solution. There was no difference between the efficacy of ORS solutions containing less than 75 mEq/l of sodium and that of an ORS solution containing 75 mEq/l of sodium, even on unidirectional tests of significance.

In conclusion, reduced osmolarity ORS solutions (215–245 mOsm/l) with 60–75 mEq/l of sodium and 75–90 mmol/l of glucose are safe for children with non-cholera diarrhea. When compared with standard ORS solution, these solutions were associated with reduced stool output, reduced vomiting and, especially, reduced need for unscheduled IV therapy. With regard to reduced stool output and reduced vomiting, this benefit may be somewhat greater for solutions with <75 mEq/l sodium (210–260 mOsm/l) than for the solution with 75 mEq/l sodium (245 mOsm/l). However, in terms of reduced need for unscheduled IV therapy, the benefit was similar for solutions with 75 mEq/l sodium—and for those with <75 mEq/l sodium.

Children with cholera

Multicentre trial of 75 mEq sodium, 75 mmol glucose ORS

A small subgroup of patients enrolled in the multicentre study (9%) had culture-proven cholera¹⁰. The safety and efficacy of a reduced osmolarity ORS solution in those children was evaluated. The need for unscheduled IV fluids, although higher than in children with non-cholera diarrhea, was lower in children treated with a reduced osmolarity ORS solution than in the children receiving standard ORS (30% in children treated with reduced osmolarity ORS solution vs. 44% in children treated with standard WHO ORS). Although mean serum sodium in children with cholera was lower after 24 hours than in children without cholera (131 mEq/l in children with cholera vs. 137 mEq/l in children without cholera), the mean difference between children with cholera treated with reduced osmolarity ORS solution (130mEq/l) and those treated with standard ORS solution (132mEq/l) was small.

In conclusion, reduced osmolarity ORS solutions (245–268mOsm/l) containing 70–75 mEq/l of sodium and 75–90 mmol/l glucose were at least as effective as standard ORS for children with cholera and, although further data should be obtained during routine use, appeared to be safe.

Combined analysis with earlier trials

The data on children with cholera who were given a reduced osmolarity ORS ^{11,12} was pooled. Results showed there was a small, but statistically significant reduction, in mean serum sodium at 204 hours in patients receiving reduced osmolarity ORS solution when compared to those given standard ORS solution. Children in these studies who developed hyponatremia did not become symptomatic. Stool output at 24 hours was not different between treatment groups in children with cholera in the multicentre study. In the other two studies, however, stool output was reduced by about 30% in children with cholera who were treated with reduced osmolarity ORS solution.

Conclusions

The studies' results, as well as an evaluation of possible economic benefits of using a reduced osmolarity ORS solution in place of standard ORS solution, was reviewed at an expert consultation, facilitated by WHO and UNICEF on July 18, 2001 in New York.

A review of the studies' findings resulted in the following conclusions:

1. The efficacy of glucose-based ORS solution for treatment of children with acute non-cholera diarrhea is improved by reducing sodium to 60–75 mEq/L, glucose to 75–90 mmol/L, and total osmolarity to 215 to 260 mOsm/L. Solutions containing 70–75 mEq/L of sodium and 75–90 mmol/L of glucose for a total osmolarity of 245 to 260 mOsm/L (the only ones tested in children with cholera) also appear to be safe and effective for use in children with cholera. Overall, in children admitted to the hospital with diarrhea, reduced osmolarity ORS solution, when compared to WHO ORS solution, is associated with fewer unscheduled IV infusions, smaller stool volume post randomization, and less vomiting. In comparison with WHO ORS solution, no additional risk was detected in developing hyponatremia.

2. A total of 14,000 deaths per million episodes of diarrhea would be avoided with moderate dehydration would be avoided with the reduced osmolarity ORS solution, by reducing the number of treatment failures. With a possible 10,000 seizures per million episodes of diarrhea with some dehydration, the estimated number of seizures per death averted would be 0.7. This could result in a cost savings of \$500 per death averted, or \$7.1 million per million episodes.

A New Recommendation

Based on these findings and recognizing that

- the programmatic and logistic advantages of using a single solution around the world for all causes of diarrhea,
- reduced osmolarity ORS solution with 60 mEq/L of sodium does not seem to be significantly better than reduced osmolarity ORS solution containing 75 mEq/L of sodium,
- reduced osmolarity ORS solution with 75 mEq/L of sodium and 75 mmol/L of glucose is effective in children with cholera, and
- safety data in patients with cholera, while limited, are reassuring,

the group of experts at the July meeting recommended using a “new and improved,” single, ORS solution (containing 75 mEq/L of sodium and 75 mmol/L of glucose, and having a total osmolarity of 245 mOsm/L) to treat children with all causes of diarrhea in developing countries.

As a result of research spanning more than 25 years, the World Health Organization (WHO) is now recommending the improved solution worldwide. The new formula reduces the need for intravenous (IV) therapy, which reduces the cost of treatment risk, thus leading to long-term economic benefits to health programs in developing countries.

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Birth of ORS

Thirty years ago researchers in Dhaka, East Pakistan (now Bangladesh) and Calcutta, India developed the use of an extraordinarily simple solution consisting of sugar, salts, and water to save the lives of severely dehydrated adults, children and infants. In 1962, scientists at the International Centre for Diarrheal Disease Research (ICDDR,B) and Johns Hopkins International Centre for Medical Research (ICMR) began work on effective therapies for diarrhea, which was claiming millions of lives globally each year. Within six years, these researchers produced and synthesized physiological evidence that overturned the medical establishment's paradigm for diarrheal disease treatment.

In 1962, when William B. Greenough arrived at the ICDDR,B and Charles Carpenter arrived in Calcutta, untreated villagers and hospitalized patients with cholera had a 30 to 40% mortality rate. Within one year the mortality rate in these hospitals was down to under one percent, with the use of a type of intravenous (IV) therapy pioneered by Dr. Robert A Phillips of the Naval Medical Research Unit in Taiwan. Within a couple of years, after Dr. Phillips came to direct the ICDDR,B, Drs. Hirschhorn, Nalin, and Cash in Dhaka simultaneously with Drs. Pierce, Mahalanabis, and Sack pioneered work on oral rehydration therapy (ORT)—the use of ORS to treat dehydration caused by diarrheal disease.

The clinical application of ORT was tested in 1968 when David Nalin and Richard Cash in conjunction with their East Pakistani colleagues tested their solution of water, glucose and salts during a cholera epidemic. The experiment was extraordinarily successful, and most of the adult male patients began to eat a normal diet of rice and curry within 3-4 hours of admission.

Also, over 80% of the scarce intravenous solution was replaced by ORT. ORT was tested more widely in a rural hospital in the Matlab district about 40 miles south of Dhaka, and was also proven successful.

Over the next few years, ORT was found effective in treating children and infants, was found useful in treating non-cholera diarrhea, and was successfully used by Dr. Mahalanabis to treat diarrhea in the refugee camps during Bangladesh's War of Independence. In 1975, UNICEF and the World Health Organization agreed to promote the worldwide use of ORT.

In the early 1980's the Bangladesh Rural Advancement Committee (BRAC) brought the message of home treatment with ORT to more than 2.5 million Bangladeshi women. Moving from door to door, health workers explained to mothers how to create ORS out of ingredients that were available in nearly every household: salt (lobon), molasses (gur) and water.

Studies in the 1990's in Bangladesh at the ICDDR,B as well as in Brazil, India, Indonesia, Peru, Viet Nam, and later in Egypt have led to the development of an ORS solution that is lower in salt and overall osmolarity. This new ORS solution reduces diarrhea and vomiting and also reduces treatment failures that require supplemental IV therapy.

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