Oral Rehydration Therapy: New Insights on an Old Remedy

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ABSTRACT

Oral Rehydration Therapy (ORT) has been the cornerstone of diarrheal management since the late 1960s. It is a cheap but effective treatment and has significantly decreased the morbidity worldwide from diarrhea-associated dehydration. The road leading to the discovery of ORT and the modifications that were done after 25 years of use are discussed in the present review.

History of ORS development

Oral rehydration therapy (ORT) has been at the forefront of diarrhea management, especially in children. It is the administration of fluid by mouth to prevent or correct the dehydration that is a consequence of diarrhea.[1] It was 30 years ago when the first clinical use of oral rehydration solution (ORS) was published. The development of ORS revolutionized diarrheal management and overturned the existing medical establishment's ideal. This change had a profound impact on mortality due to diarrhea, particularly in children in developing countries. However, the road leading to this innovation was difficult. The simplicity of ORT contrasts starkly with the story of its discovery, characterized by "abrasive personalities, professional jealousies, scientific breakthroughs and an unusual degree of scientific cooperation", as well as "determination, intuition, and serendipity".[2]

In the 1940s and 50s, there was a preference for intravenous solutions and the use of oral solutions was considered scientifically unsound. Diarrhea management involved parenteral administration of electrolyte solutions, blood transfusions, fasting ("bowel rest") and gradual reintroduction of feeding after the "starvation period". During this time, Dr. Daniel Darrow did groundbreaking electrolyte studies and advocated rehydration solutions (parenteral and oral) with the use of sodium chloride, potassium and glucose to replace stool losses. However, glucose was perceived as a source of calories and not for its sodium absorption-enhancing effect. Oral treatment was considered an intermediate step between intravenous therapy and feeding. It was in the 1950s when physiologists elucidated on glucose, sodium, and water transport, and hypothesized that sodium and glucose were co-transported along the intestinal mucosa.

In September 1961, following a cholera pandemic in the Philippines, Dr. Robert Philips sent a team from the Naval Medical Research Unit (NAMRU-2) in Taiwan to treat patients in San Lazaro Hospital. Use of parenteral cholera treatment consisting of oral electrolyte solution with glucose resulted in a low mortality rate of 3.4%. The choice of glucose was to help maintain an isosmolar solution, since the solution contained less sodium, and not to enhance absorption. Nevertheless, Dr. Philip's work first demonstrated that oral therapy could be viable. On August 4, 1962, Dr. Philips successfully treated three cholera patients with a potent oral electrolyte solution containing high concentrations of glucose and sodium. A clinical trial was performed in September 1962 involving 30 patients. Five patients died due to fluid overload since the ORS used was three times isotonic and intravenous fluids (IVF) were co-administered. The following four years slowed down ORS research and was even threatened by Dr. Philip's setback.

Eventually, in the mid 1960s, initial work on ORT in Dacca, East Pakistan (now Bangladesh), and Calcutta, India, from individuals coming from powerful US institutions—Johns Hopkins, Harvard, the Center for Disease Control, the United States Navy, and the National Institutes of Health laid down the foundation for ORT use and provided a physiologic basis for its role in clinical medicine, particularly in the treatment of cholera. Smaller clinical trials in the late 1960s conducted by Hirschhorn, Nalin, Cash, and Pierce confirmed the effectiveness of adding glucose to sodium chloride solutions for ORT, culminating in 1968 with the first official publication on the clinical use of ORT.[3] In 1971, the Indo-Pakistani war sparked a health emergency in refugee camps when cholera outbreaks caused high mortality and dwindling supplies of IVF. ORS sachets were distributed to over 3,000 adult cholera patients with only a 3% death rate (vs. 20 to 30% in those camps using IVF). Later studies proved the effectiveness of ORT even in children and in non-cholera cases. It was in 1978 that the WHO, through its

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Control of Diarrhoeal Disease Programme, began to globally recommend the use of ORT to treat and prevent dehydration. It is estimated that more than one million deaths could have been averted annually with ORT. It is not surprising that the physiological basis behind ORS has been hailed as "potentially the most important medical advance of the century".[4]

WHO Recommended ORS

ORS 311. The use of the WHO-recommended ORS with 90 mmol/l of sodium and an osmolality of 311 (ORS 311) gained wide acceptance, and for more than 25 years has proved to be effective and safe, especially in developing countries. However, this met resistance in developed countries because of the concern with high sodium and, consequently, high osmolarity. In addition, ORS can only treat and prevent dehydration but does not reduce stool output and duration of diarrhea. A search for improved ORS began in the 1980s with the following criteria: it should be safe and effective in all types of diarrhea; could reduce stool output; and could offer other clinical benefits, including a decrease in the duration of diarrhea.[5]

Two approaches were done in the improvement of ORS. One was modifying the amount and type of organic carriers to promote intestinal absorption of sodium and water such as replacing glucose with complex carbohydrates (maltodextrins or glucose polymers, rice powder), amino acids, or combining glucose with amino acids. The other was reducing the osmolarity of ORS to avoid the adverse effects of hypertonicity on net fluid absorption by replacing glucose with complex carbohydrates and reducing the concentration of glucose and sodium.

In 1994, the WHO/UNICEF Expert Panel Meeting[6] concluded that ORS with amino acids or maltodextrins were not sufficiently effective or practical to replace ORS 311. Rice-based ORS significantly reduced stool output and duration of diarrhea versus standard ORS in cholera (adults and children). Rice-based ORS was not superior compared with ORS 311 in children with acute, non-cholera diarrhea, especially if feeding was started soon after rehydration. In a recent review on polymer-based ORS,[7] which included 34 randomized controlled trials, its use resulted in fewer unscheduled intravenous infusions and, similar to the WHO conclusion, shorter duration of diarrhea among adult cholera cases.

Reduced osmolality ORS. In 2001, Hahn and colleagues[8] published their meta-analysis on reduced osmolarity ORS in children with acute, non-cholera diarrhea and concluded that its use was associated with a significant reduction (about 35%) in the need for unscheduled IV therapy and vomiting (about 35%). There was a trend towards reduced stool output (20%) and greater, though not significantly greater, incidence of hyponatremia in reduced osmolarity ORS. Because of this study and after considering all available data,[5] the WHO/UNICEF in their consensus statement in 2004[9] concluded 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 total osmolarity to 215–260 mOsm/l. However, they recommended that the policy of a single solution be maintained and that this new ORS should contain 75 meq/l of sodium and 75 mmol/l of glucose and have a total osmolarity of 245 mOsm/l. Table 1 shows the comparison of ORS 311 and reduced osmolality ORS formulations.

The concern regarding hyponatremia using the new ORS formulation was investigated in studies done in Bangladesh[10] and Indonesia.[11] The Bangladesh study showed minimal occurrence of hyponatremia and a significant reduction in children developing seizures due to hyponatremia with the use of reduced as compared with the ORS 311 formulation. In the study in Indonesia among cholera patients, there was no effect on serum sodium on the 24th hour following rehydration.

Table 1. Composition of ORS 311 and reduced osmolality ORS formulation (meq or mmol/l)

	ORS 311	Reduced ORS
Glucose	111	75
Sodium	90	75
Chloride	80	65
Potassium	20	20
Citrate	10	10
Osmolarity	311	245

Adjunct treatment of acute diarrhea

Commercially prepared ORS solutions using the reduced ORS formulation are currently available in the market. This, along with zinc supplementation, has gained recognition universally as the primary management strategy for acute childhood diarrhea. Zinc-fortified ORS as compared with ORS alone or with zinc syrup resulted in a lower proportion of children with watery stools.[12] Use of zinc with ORS has also been shown to reduce the total cost and duration of acute diarrhea.[13]

Aside from routine zinc supplementation, adjunct therapies such as probiotics are now increasingly becoming popular, although concomitant use of zinc or probiotics with ORS remain investigational. A meta-analysis[14] of 23 studies showed that probiotics decreased the mean duration of diarrhea by 30 hours and reduced the risk (RR=0.66) of diarrhea on day 3 when given to patients with presumed infectious etiology.

No matter what additional therapies for childhood diarrhea have and will emerge, ORT will remain the mainstay of treatment. It has proved its worth as an effective, safe, cheap and readily available treatment based on sound physiologic principles. It is a cost-effective strategy with great impact in improving child survival.

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