Review article

ORT in diarrhoea: An overview

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Abstract: This paper attempts to summarize the development of ORT (Oral Rehydration Therapy) and its role as the major public health intervention for the control of diarrhoeal diseases. It also highlights the large number of scientific studies conducted to assess the safety and efficacy of ORS (Oral Rehydration Solution). Improved ORS formulations trial including hypoosmolar solutions are described as these are areas of recent clinical studies that address the drawbacks in WHO/UNICEF ORS. However, until new ORS formulations are evaluated and implemented, the present glucose-based ORS does still save millions of lives and need to be recommended for all forms of dehydrating diarrhoea. [*Ethiop. J. Health Dev.* 199-;0(0):0-00]

Introduction

Diarrhoeal diseases are leading causes of morbidity and mortality in children in developing countries. Since the discovery of ORS and its promotion by WHO and UNICEF, for rehydration of patients with acute watery diarrhoea, millions of lives have been saved world wide (1). ORS contains glucose (anhydrous) (20g) and three salts - sodium chloride (3.5g), trisodium citrate dihydrate (2.9g) or sodium bicarbonate (2.5g), and potassium chloride (1.5g) to be mixed in one litter of drinking water. This mixed solution can be used safely within 24 hours of its preparation for prevention and/or correcting dehydration at home or at any level of health care delivery. Currently, ORS alone can rehydrate over 90% of patients with some dehydration (2). Hospital admission rate for treatment of diarrhoea has also been reduced by 50% after the introduction of ORT (3). Presently, the WHO oral rehydration salt solution (ORS) is the least expensive health intervention widely accepted for treating dehydrating diarrhoea in all age groups (4).

History of ORT

Intravenous therapy (I.V.) was the main stay of treatment for correction of diarrhoeal dehydration before the development of oral rehydration solution. In 1832 an oral salt solution that was given to an adult cholera patient actually worsened diarrhoea (5). On the other hand, Leonardo Roger (6) in 1890 used hypertonic saline and reduced the hospitalized cholera mortality from 61% to 33%. Further attempt was made to improve I.V. therapy by adding bicarbonate and sodium and gradually between 1960-1970 hypertonic saline was totally replaced by isotonic saline (7, 8).

In animal experiments, a group of scientists observed that glucose enhances the transport of sodium and water across the intestinal brush border membrane (9-11). Gangarosa et al. (12) in 1960 observed that no morphologic changes occur in the gut epithelium of cholera patients during the infection which further indicated the probability that sodium glucose coupled absorption was intact. In early 1960 Robert Phillips showed that glucose when added to oral perfusions could produce a positive fluid balance in purging cholera patients (13). These two important clinical and physiological observations laid down the scientific basis of the discovery of oral rehydration therapy. In the late 1960s, studies in Dhaka (Bangladesh) and Calcutta (India) defined the parameters for a

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successful development of oral rehydration salt (ORS) solution. This formulation was later standardized and put to global use by WHO and UNICEF.

Clinical Trials of ORT

The sodium-glucose coupled transport system which remained intact in diarrhoeal disorders secondary to organisms secreting enterotoxins (*E. coli, V.Cholerae*) paved the way for major clinical trials. During 1965-1969 Pierce et al. (14) and others (15-17) first attempted to show the beneficial role of ORS. When cholera epidemic broke out among refugees in India during the Bangladesh liberation war, the introduction of ORS in case management by Mahanalabis et al. (18) clearly showed marked reduction in case fatality with minimum health intervention. In 1978 Sircar et al. (19) also used ORS successfully in managing a large scale cholera epidemic in Manipur (India). Other two studies also showed that ORS is effective for treating children with diarrhoea including cholera (20, 21). On the basis of all these information, the World Health Organization started global diarrhoeal diseases control programme with ORT as its main strategy for preventing diarrhoeal mortality rate in 1978.

The following year, an issue was raised whether WHO-ORS (N^+ 90 mmol/l) is safe and effective for treating neonatal diarrhoea. However, Pizarro along with his colleagues from Costa Rica (22, 23) showed that WHO-ORS was also effective for the treatment of neonates with dehydrating diarrhoea and safe if it was used along with plain water in 2:1 regimen. But this 2:1 regimen was very confusing to illiterate mothers of developing countries. Subsequently, Roy et al (24) and Dutta et al. (25) showed that uninterrupted breastfeeding along with ORS is safe and is easy to follow. The use of ORS with a sodium concentration of 90 mmol/L was also a point of concern among some pediatricians. This issue was later resolved by clinical studies that confirmed that WHO-ORS containing 90 mmol/L of sodium as physiologically sound and clinically safe, and an ideal fluid in the management of hyponatremia and hypernatremia (26). The efficacy and safety of WHO-ORS in malnourished children was also reported by Dutta et al. (27).

Drawbacks of ORS

The major drawbacks of WHO-ORS are that (1) it does not shorten the duration of diarrhoea, (2) it does not reduce the fluid requirements. These disadvantages, resulting in reduced acceptability by mothers and health workers, may be the frequent causes for the abuse of antibiotics and antidiarrhoeals in developing countries. Moreover, its efficacy cannot be enhanced by increasing the glucose concentration in ORS. Hence, there is a big concern to improve this formula or search for a new agent which will overcome the drawbacks of ORS either by stimulating the reabsorption of endogenous secretion from the intestine or by diminishing the secretion into the intestine.

Super ORS and cereal-based ORS

In the early eighties, encouraged by promising results from few clinical trials, the Control of Diarrhoeal Diseases Programme of the World Health Organization started supporting research proposals to develop improved ORS formulations. Simultaneously several investigators around the globe began independent evaluations of the improved ORS formulations. It was demonstrated that certain amino acids (glycine, alanine) can enhance the absorption of sodium and water from the gut by independent pathway of glucose mediated sodium absorption. Similarly, certain cereal preparations (e.g. maltodextrin) were found to liberate glucose slowly from starch during digestion thus promoting sodium absorption, as in the glucose ORS. Use of different cereals (particularly rice) in place of glucose in ORS formulations were proposed and studied in many countries. With these new concepts new oral solutions were developed which were known as "Super ORS" (28, 29). In clinical studies, however, Nalin Et al. (30) and Patra et al. (31) showed that glycine fortified ORS reduces the duration of diarrhoea by 28% and 30% and reduces stool volume by 70% and 50%, respectively. On the other hand, studies by Bhattacharya et al. (32) and Santosham et al (33) showed that glycine fortified ORS does not reduce the stool volume and rather may induce hypernaetremia in young children. In 1989, Patra et al. (34) demonstrated that alanine fortified ORS reduces the stool volume in adult patients with acute diarrhoea, while Ribeiro et al. (35) could not substantiate this observation in children with diarrhoea.

Although all these findings were conflicting, it may be concluded that this approach may have some advantages in treating cholera and diarrhoea caused by other toxigenic bacteria, but it was not more effective than the standard ORS solution for patients with diarrhoea of more diverse etiology, particularly in infants. Use of starch (maltodextrin) in ORS solution was also found to show no appreciable additional benefit compared to the standard ORS solution.

Patra et al. (36) from Calcutta and Molla et al. (37) from Dhaka reported that cooked rice ORS reduces stool volume in patients with acute diarrhoea by 49% and 28%, respectively. Several scientists (38) undertook similar studies with cooked rice ORS from different parts of the world. In 1992 Gore et al. (39) in a meta-analysis of 13 clinical trials, showed that rice-ORS solution significantly reduced the rate of stool output during the first 24 hours by 36% (95% CI 28 to 44%) in adults with cholera and by 32% (95% CI 19 to 45%) in children with cholera. The rate of stool loss in infants and children with acute non-cholera diarrhoea was also reduced by 18% (95% CI 6 to 30%).

Hypoosmolar ORS

Recent studies of Sandhu et al. (40), Elliot (41) and Farthing (42) using animal models and human perfusion techniques demonstrated that optimal water and salt absorption may be achieved by using a hypotonic salt solution rather than an isotonic salt solution because the former results in greater intestinal water absorption, induces rapid gastric emptying making the ORS available to the jejunum for maximum glucose stimulated sodium and water absorption. In a recent open clinical trial conducted in Finland, it was found out that an oral hypotonic ORS (osmolality 224 mosmol/l) was superior than isotonic ORS (osmolality 304 mosmo/l) for the treatment of children with dehydrating diarrhoea. Children who received hypotonic ORS had significantly fewer stool, shorter duration of diarrhoea and hospital stay as compared to children who received isotonic ORS (43). A preliminary report from Egypt, of using hypoosmolar ORS (210 mosmol/l), also showed better improvement in clinical features (stool output, fluid intake) than standard ORS (44). In order to assess the efficacy hypoosmolar ORS in acute diarrhoea, a large multicenter study is now underway in several countries (Brazil, India, Mexico, and Peru) (44).

Short-chain fatty acids (SCFA)

Short-chain fatty acids are the principal end products of fermentation of unabsorbed carbohydrates in the colon. Initially, it has been suggested that short-chain fatty acids may contribute to diarrhoea. However, it is now clear that short-chain fatty acids are absorbed from the colon and stimulate salt and water absorption (45, 46). Ramakrishna and Mathan (47) showed that the concentration of and output of short-chain fatty acids (SCFA) in faeces in patients with acute watery diarrhoea (including cholera) is reduced and that the addition of luminal SCFAs can reverse the impairment of colonic absorption. As a result, they are suggesting addition of SCFAs in ORS as an alternative approach for treatment of dehydrating diarrhoea in the future.

Conclusion

The discovery of oral rehydration therapy for the treatment of dehydrating diarrhoea was the most important medical advance of this century. The invaluable clinical studies and their results have clearly indicated glucose based ORS as an important tool in the management of dehydrating diarrhoea. It is the most powerful and least expensive child survival intervention. Although oral rehydration solution with the present formula saves millions of lives, it does not reduce the volume, frequency, or duration of diarrhoea. These improved ORS formulas incorporated the addition of certain aminoacids (glycine, alanine, glutamine etc) and/or replacement of the glucose by cereals (rice, maize, wheat etc) with very limited and conflicting results. Of all the clinical trials so far, rice-ORS has shown reduction in the rate of stool output in cholera patients. As the vast majority of patients visiting clinics are young children with non-cholera diarrhoea, and as rice-ORS requires increased cost for cooking, its wide spread promotion is not justified at the present time. Although there are considerable reports of SCFAs on the enhancement of sodium and water absorption from the gut, no ample evidences are available to show their beneficial role and their contributions in improved ORS formula. The role of hypoosmolar ORS in the treatment of acute diarrhoeal diseases needs further more clinical trials and critical evaluations from developing countries where the problem of diarrhoeal illness is still prevalent.

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