Indian J Med Res 160, July 2024, pp 6-9
DOI: 10.25259/IJMR_989_2024

Quick Response Code:

Editorial

Development of oral rehydration salt solution: A triumph of medical science

Oral rehydration salt solution (ORS) stands as one of the most significant medical advancements of the 20th century, revolutionizing the treatment of dehydration caused by diarrheal diseases. This simple yet groundbreaking solution has saved millions of lives, particularly in low-income countries where diarrheal diseases are a leading cause of mortality, especially among children[1]. Consequently, *The Lancet* identified oral rehydration therapy (ORT) as "the most important medical advance of the 20th century"[2]. The development of ORS is a story of innovative science, dedicated researchers, and the transformative impact of collaborative efforts, particularly the pivotal roles played by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b; formerly known as Cholera Research Laboratory or CRL) and Johns Hopkins University International Center for Medical Research and Training in Calcutta, India[3].

The genesis of oral rehydration therapy

Oral rehydration therapy (ORT) emerged from the understanding that intestines could absorb fluids with the right balance of salts and glucose even during severe dehydration[4]. This breakthrough offered a simple, effective method to treat dehydration and reduce the need for intravenous (IV) fluids. ORS originated in the 1960s during rampant cholera outbreaks in the Indian subcontinent. Cholera, caused by the bacterium *Vibrio cholerae*, leads to severe dehydration and can be fatal if untreated. At that time, IV therapy was the primary treatment for dehydration, but it was not readily available in resource-limited settings due to the need for sterile equipment and trained medical personnel.

Pioneering research and early discoveries

The story of the development of ORS began with the sufferings of patients with diarrheal dehydration, which spurred researchers to develop more accessible rehydration treatments. Dr Daniel Darrow's electrolyte studies[5] in the 1940s at Yale University were pivotal. He emphasized the importance of precise electrolyte replacement in treating dehydration, reducing infant mortality from severe dehydration to below five per cent. His work laid the groundwork for what would evolve into ORT. However, Darrow saw oral rehydration as a transitional measure, differing from the more straightforward yet effective approach that would later be recognized in Dhaka and Calcutta.

In the 1950s, research by R.B. Fisher and D.S. Parsons on glucose transport in the intestine[6], and subsequent studies by Schultz and Curran at the Harvard Biophysics Laboratory, provided foundational knowledge on the coupling of sugar and salt absorption[7,8]. These physiological insights were crucial, but they did not directly address the immediate need to treat diarrheal dehydration in practical, resource-limited settings.

Field trials and the birth of ORS

The 1960s witnessed intense research and field trials that brought ORS closer to reality. In September 1961, during a cholera outbreak in the Philippines, Dr Robert A. Phillips experimented with oral rehydration, adding glucose to enhance sodium absorption[3]. Despite initial setbacks, Phillips's work highlighted the potential for oral therapies. His cautious advocacy for rigorous validation through balance studies set the stage for future breakthroughs[3].

Establishing the Pakistan-SEATO Cholera Research Laboratory (CRL) in Dhaka in December 1960 marked a turning point[9]. Later renamed as the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) after Bangladesh's independence, the laboratory initially focused on improving IV treatments for cholera. This led to the development of the 5:4:1 IV solution (Dacca Solution), which contained 5 g of sodium chloride, 4 g of sodium bicarbonate, and 1 g of potassium chloride in one litre of pyrogen-free distilled water[10]. However, researchers soon recognized the impracticality of these methods in resource-limited settings[9]. Norbert Hirschhorn and

David Sachar conducted crucial experiments showing that a simple glucose-based solution could reduce stool output in cholera patients, demonstrating the gut's ability to absorb fluids and electrolytes[11]. Despite initial scepticism, these findings gradually gained acceptance for their life-saving potential, especially in areas lacking intravenous resources.

The role of the Johns Hopkins Center for Medical Research and Training in Calcutta

In 1967, the Johns Hopkins Center for Medical Research and Training in Calcutta made ground breaking progress in advancing ORT. Led by Nathaniel F. Pierce, the Calcutta team improvised Norbert Hirschhorn's work by perfusing glucose solutions intra-gastrically at variable rates matching or exceeding stool output[12]. The findings demonstrated that cholera patients could maintain hydration solely with intragastric glucose solutions, eliminating the need for additional IV therapy[12,13]. This marked a significant departure from the fixed-rate approach used in Dhaka and underscored the potential of ORT as a practical and scalable solution.

Despite these strides, practical advancements in ORT slowed as researchers awaited further validation. A cholera outbreak in East Pakistan in late 1967 prompted further field trials. Drs David Nalin, Richard Cash, Rafiqul Islam, and Majid Molla refined their protocols based on intake-output dynamics, leading to a successful demonstration in the Cholera Research Laboratory hospital in Dhaka[3]. By April 1968, they had shown that oral glucose-sodium solutions could effectively maintain electrolyte balance in cholera patients, reducing IV fluid requirements by 80 per cent[14]. The discovery of ORS was a collaborative global effort akin to a relay race in which each runner's contribution remains crucial. The collaboration and knowledge exchange among scientists from various nations were pivotal in developing this life-saving treatment.

From laboratory success to field implementation

The findings from Dhaka, published in *The Lancet* in August 1968, affirmed that ORT could replace a significant portion of IV therapy in treating acute cholera in adults[14]. The next challenge was proving ORT's practicality in rural settings where IV therapy was inaccessible. The CRL devised a protocol for ORT to be implemented in *Matlab Bazaar*, in rural East Pakistan (later became Bangladesh), demonstrating its efficacy in rehydrating cholera patients in primitive settings[3]. Their success extended ORT's application beyond cholera to non-cholera diarrheal illnesses and paediatric dehydration, solidifying its status as a groundbreaking treatment. In addition, field studies in *Matlab* demonstrated the extension of diarrhoea management in the community using ORS with safety and efficacy[15,16].

The catalyst: Dilip Mahalanabis and the Bangladesh War of Independence

ORT gained perhaps its most significant practical success during the Bangladesh War of Independence. Dr Dilip Mahalanabis pioneered the use of ORT in the refugee camps near Calcutta bordering Bangladesh. Unlike controlled environments, Mahalanabis implemented ORT under dire circumstances where family members administered the solution. This approach not only demonstrated ORT's effectiveness in emergencies but also directly saved lives. The impact on saving lives was profound, catalyzing global recognition and adoption of ORT as a viable treatment for diarrheal diseases[17].

Mahalanabis' initiative highlighted ORT's adaptability and efficacy beyond controlled research settings, proving its utility in real-world crisis scenarios. His work resonated deeply with public health leaders like Langmuir, who acknowledged its pivotal role in expanding ORT's reach and impact. While Nalin, Cash, Islam, Rahman, and Yunus's foundational work laid the groundwork, Mahalanabis' emergency response provided a compelling demonstration that accelerated ORT's acceptance and integration into global health strategies.

Global recognition and ongoing challenges

By the early 1970s, efforts by Nalin, Cash, Mahalanabis, and Dhiman Barua advanced the validation of ORT across diverse patient demographics and diarrheal conditions. This period marked a turning point, cementing ORT as a cornerstone of modern diarrheal disease management, supported by organizations like United Nations Children's Fund (UNICEF) and World Health organization (WHO). Mahalanabis' work underscored ORT's transformative potential, saving lives and setting a precedent for emergency medical interventions worldwide. In Dhaka, Majid Molla, Ayesha Molla, Asma Islam, and Greenough conducted trials on cereal-based ORS, highlighting rice-based ORS as particularly promising[18,19]. Currently, clinicians advocate for ORS in treating dengue fever due to plasma leakage leading

to hemo-concentration, hypovolemia, and shock[20]; despite WHO guidelines, further research is needed due to insufficient evidence[21] in this clinical condition. Challenges to ORS implementation include a lack of awareness, cultural practices, and misconceptions about diarrhoea treatment. Addressing the underlying causes of diarrheal diseases, poor sanitation, lack of clean water, and access to effective vaccines against rotavirus and cholera is crucial. The low-sodium ORS for children with severe acute malnutrition (SAM), REhydration SOlution for MALnutrition (ReSoMaL) is not appropriate for those with severe cholera. Therefore, identifying an effective alternative for SAM children experiencing severe diarrhoea is essential[22].

Conclusion

Oral rehydration salt solutions represents a triumph of simple and effective medical intervention. The discovery and implementation of ORS have transformed the treatment of dehydration caused by diarrheal diseases, saving about 70 million lives worldwide. The pioneering work of David Nalin, Richard Cash and Dilip Mahalanabis, along with the pivotal roles of other scientists of icddr,b and the International Centre for Medical Research and Training (ICMRT), Calcutta have been instrumental in this global health success story. As we look to the future, continued efforts to promote ORS, improving its efficacy by altering its composition, improved sanitation measures, and addressing the underlying causes of diarrheal diseases are essential. By building on the legacy of ORS and the work of these dedicated researchers and institutions, we can continue to make strides in reducing child mortality and improving global health. Finally, the use of ORS is likely to continue indefinitely, as the complete elimination of diarrheal illness may never be achievable.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

***Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation*:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

Mustafa Mahfuz[1*], A.K.M. Tariful Islam Khan[2] & Mohammad Yunus[3]

Divisions of [1]Nutrition Research, [2]Development and Communications, & [3]Maternal and Child Health, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, 1212, Bangladesh

[*]*For correspondence*: mustafa@icddrb.org

Received July 16, 2024

References

1. Dadonaite B. *Oral rehydration therapy: a low-tech solution that has saved millions of lives*. Available from: *https://ourworldindata.org/oral-rehydration-therapy*, accessed on July 10, 2024.
2. Santosham M, Chandran A, Fitzwater S, Fischer-Walker C, Baqui AH, Black R. Progress and barriers for the control of diarrhoeal disease. *Lancet* 2010; *376* : 63-7.
3. Ruxin JN. Magic bullet: The history of oral rehydration therapy. *Med Hist* 1994; *38* : 363-97.
4. World Health Organization. Institutional Repository for Information Sharing. *The treatment of diarrhoea: A manual for physicians and other senior health workers*. Available from: *https://iris.who.int/handle/10665/43209,* accessed on July 9, 2024.
5. Darrow DC, Pratt EL. Disturbances of water and electrolytes in infantile diarrhoea. *Pediatrics* 1949; *3* : 129-56.
6. Fisher RB, Parsons DS. Glucose movements across the wall of the rat small intestine. *J Physiol* 1953; *119* : 210-23.
7. Schultz SG, Fuisz RE, Curran PF. Amino acid and sugar transport in rabbit ileum. *J Gen Physiol* 1966; *49* : 849-66.
8. Curran PF, Schwartz GF. Na, Cl, and water transport by rat colon. *J Gen Physiol* 1960; *43* : 555-71.
9. ICDDR, B and ORS: the history of a miracle discovery. *Glimpse* 1994; *16* : 3-4.
10. Greenough WB 3rd, Gordon RS Jr, Rosenberg IS, Davies BI, Benenson AS. Tetracycline in the treatment of cholera. *Lancet* 1964; *1* : 355-7.
11. Hirschhorn N, Kinzie JL, Sachar DB, Northrup RS, Taylor JO, Ahmad SZ, *et al.* Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. *N Engl J Med* 1968; *279* : 176-81.
12. Pierce NF, Banwell JG, Mitra RC, Caranasos GJ, Keimowitz RI, Mondal A, *et al.* Oral maintenance of water-electrolyte and acid-base balance in cholera: a preliminary report. *Indian J Med Res* 1968; *56* : 640-5.
13. Pierce NF, Banwell JG, Rupak DM, Mitra RC, Caranasos GJ, Keimowitz RI, *et al.* Effect of intragastric glucose-electrolyte infusion upon water and electrolyte balance in Asiatic cholera. *Gastroenterology* 1968; *55* : 333-43.
14. Nalin DR, Cash RA, Islam R, Molla M, Phillips RA. Oral maintenance therapy for cholera in adults. *Lancet* 1968; *2* : 370-3.

15. Chen LC, Black RE, Sarder AM, Merson MH, Bhatia S, Yunus M, *et al.* Village-based distribution of oral rehydration therapy packets in Bangladesh. *Am J Trop Med Hyg* 1980; *29* : 285-90.
16. Snyder JD, Yunus M, Wahed MA, Chakraborty J. Home-administered oral therapy for diarrhoea: A laboratory study of safety and efficacy. *Trans R Soc Trop Med Hyg* 1982; *76* : 329-33.
17. Mahalanabis D, Choudhuri AB, Bagchi NG, Bhattacharya AK, Simpson TW. Oral fluid therapy of cholera among Bangladesh refugees. *Johns Hopkins Med J* 1973; *132* : 197-205.
18. Molla AM, Sarker SA, Hossain M, Molla A, Greenough WB 3rd. Rice-powder electrolyte solution as oral-therapy in diarrhoea due to *Vibrio cholerae* and *Escherichia coli*. *Lancet* 1982; *1* : 1317-9.
19. Molla AM, Ahmed SM, Greenough WB 3rd. Rice-based oral rehydration solution decreases the stool volume in acute diarrhoea. *Bull World Health Organ* 1985; *63* : 751-6.
20. Simmons CP, Farrar JJ, Nguyen V, Wills B. Dengue. *N Engl J Med* 2012; *366* : 1423-32.
21. Dengue: Guidelines for diagnosis, treatment, prevention and control: New edition. Geneva: World Health Organization; 2009.
22. Alam NH, Hamadani JD, Dewan N, Fuchs GJ. Efficacy and safety of a modified oral rehydration solution (ReSoMaL) in the treatment of severely malnourished children with watery diarrhea. *J Pediatr* 2003; *143* : 614-9.