ORAL REHYDRATION THERAPY, A ‘SIMPLE SOLUTION’ :
HISTORY AND GLOBAL APPLICATION*

DILIP MAHALANABIS**

My friends often asked me to write my own account on the development of ORT and its global implementation. I hesitated so long partly due to my preoccupation with my ongoing work and partly my desire not to offend some of my friends competing among themselves for credit who were involved with the development of ORT. As time passed, I note considerable asymmetry on information, loss of information and distortion of information on the history of ORT development. The last one is partly due to rationalization of events by many as the time passed by. I should add, writing history of events in which I was a part, makes it difficult. In this paper, I have tried to be as objective as possible yet it should be treated as an account from my personal and professional point of view and I am responsible for omissions and inaccuracies. I start with a summary of relevant physiological studies, the relevant clinical studies on proof of concept, clinical application and randomized Clinical Trials with ORT diarrhoea and finally its application among war refugees from Bangladesh under the most difficult field condition.

Glucose, Sodium and Water Transport

Physiologists have long studied the relationship between glucose and sodium absorption from the small intestine. Some examples of these research efforts relevant to the development of ORT include the following: (1) In 1902, Waymouth Reid, a Scottish physiologist, demonstrated enhanced sodium absorption in the presence of glucose by the mammalian small intestine using dog intestinal loops; (2) Barany and Sperber, in 1939, and Fisher and Parsons, in 1953, confirmed these findings using rabbit small intestine; (3) Riklis and Quastel showed in 1958 that sodium ion was linked to glucose absorption, and Schultz and Zalusky described the mechanism of this linkage; (4) Schell and Clifton, in 1963, using intestinal intubation techniques in human volunteers, demonstrated a dramatic improvement in sodium chloride and water absorption from Ringer’s solution in both the jejunum and ileum with the addition of 1 g% glucose; (5) Subsequently, in vivo studies in normal human small intestine defined the quantitative relationships of glucose with enhanced sodium and water absorption. More recently, it was hypothesized that this intestinal glucose-facilitated absorption of sodium and water from the small intestinal lumen remained largely intact during cholera. Philips first validated this approach in a few profusely purging adult cholera patients. In contrast to his earlier studies in which an oral electrolyte solution but without glucose, did not lead to net absorption of the fluid, the glucose containing electrolyte solution was absorbed from the small intestine and led to a net positive fluid and sodium balance. Deaths occurred during these early trials of oral therapy, however, and Phillips did not believe that a practical form of therapy had been discovered. Nevertheless, this demonstration may be regarded as the beginning of the scientific development of oral rehydration therapy for cholera and subsequently for all diarrhoas.

Subsequently, Pierce in Calcutta and Hirschhorn in Dhaka (1968) evaluated isotonic oral rehydration salt solutions containing glucose and sodium in approximately equal concentrations and dramatically demonstrated the substantial decrease in the requirement for intravenous fluids, indicating that absorption was taking place across the small intestines. Studies in animal models (1968) showing that glucose mediated absorption took place in
the intestines of dogs challenged with cholera toxin helped to confirm these findings.

To be useful as a public health tool, this physiologic observation had to be extended to larger numbers of patients with both cholera and non-cholera diarrhoea. This was carried out in Dhaka by Cash and Nalin and later in refugee camps in India by Mahalanabis and colleagues. During the war of independence of Bangladesh, refugees fled across the border into India. In these conditions of poor sanitation and scarce medical resources, oral rehydration therapy was used as a matter of necessity and it performed extremely well. Case-fatality rates of about 3% were not as low as they would have been with adequate intravenous supplies; still, ORT saved most of the patients and proved that oral rehydration was a powerful tool for controlling epidemics. This helped to convince the health planners and public health workers of its obviously important role as a public health weapon.

Soon to follow were independent studies from Calcutta and Dhaka that provided additional evidence for the usefulness of ORT in cholera patients. Demonstration of the success of ORT in adult cholera patients was then followed by a series of clinical trials in children with cholera, in infants and small children with diarrhoea due to rotavirus, enterotoxigenic *E. coli* and other etiologic agents.

Another demonstration of the power and versatility of oral rehydration in a practical setting was the decrease in diarrhoea mortality following the introduction of an ORT program in a village in southern Bangladesh. Here, ORT was provided by a packet distribution program in which depot holder families maintained a supply of ORS packets and were trained how to make the solution for their neighbors. Furthermore, the village members knew where to obtain the fluids in their own village and were taught the value of rehydration. Thus, rehydration could begin at an early stage in the illness as a major therapeutic tool with the ability to correct dehydration and maintain hydration in acute diarrhoea in all but the most severe cases and in all ages regardless of etiologic agents.

Schedl and Clifton in 1963 using marker Perfusion technique in humans showed marked absorption of sodium when 1 percent glucose substituted sodium and chloride in equimolar proportions in Ringers solution both in normal subjects and those with non-tropical sprue (Celiac Disease). This study was largely ignored through it is the first demonstration of glucose mediated sodium across the small intestine both in normal subjects and in a diseased state.

**Development of I.V. Therapy for Diarrhoea in Infants and Children (Role of Daniel Darrow and Colleagues)**

Given that the Global Program was targeted to under five children, we have comment on the development of optimum I.V. therapy in infants and children. In the 1940s Dr. Daniel Darrow and colleagues conducted a series of metabolic balance study in dehydrated infants and children to estimate the amount of fluid and salt loss and developed physiologically appropriate intravenous rehydration therapy that included sodium, potassium, chloride and glucose based on net loss in moderate to severe dehydration due to diarrhea in infants and children who need I.V. therapy (Daniel Darrow et al. J. Pediatr. 1949; 3 : 129-56). He based his treatment protocol on the results of metabolic balance studies technique known as recovery balance study in dehydrated infants and children. In short, he and colleagues meticulously measured intake and output of fluid and salts in dehydrated infants during recovery until a steady state is reached that is when daily intake approximately equals the output and then calculated the net amount of water and salts retained by the body and these amounts were considered to be the net loss at the onset of treatment when the infant was admitted with tell tale signs of dehydration. The estimated deficits from severe dehydration due to acute diarrhoea in infants are given in the following table. I have added the results of a “recovery balance study on infants with severe dehydration due to cholera” we conducted (1970). This study was done to determine the magnitude of water and salt need of infants with severe dehydration associated with cholera.

**TABLE 1. Estimated Deficits for Severe Dehydration Due to Acute Diarrhoea in Infants**

<table>
<thead>
<tr>
<th>Deficits for each kg body weight</th>
<th>Water (ml)</th>
<th>Sodium (mEq)</th>
<th>Potassium (mEq)</th>
<th>Chloride (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoeal dehydration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Isotonic</td>
<td>100-120</td>
<td>8–10</td>
<td>8–12</td>
<td>8–10</td>
</tr>
<tr>
<td>• Hypotonic</td>
<td>100-120</td>
<td>10–12</td>
<td>8–12</td>
<td>10–12</td>
</tr>
<tr>
<td>• Hypertonic</td>
<td>100-120</td>
<td>2–4</td>
<td>0–4</td>
<td>-2 to -6</td>
</tr>
<tr>
<td>• Cholera* (12-24 months of age)</td>
<td>100</td>
<td>10.5</td>
<td>6.5</td>
<td>9</td>
</tr>
</tbody>
</table>

* Mahalanabis D et al. 1970

Points to note that rehydration needs in infants are closely similar between those with cholera and those with non-cholera diarrhoea. These findings supported our contention that fluid (and salts) replacement should be similar in acute infantile diarrhoea irrespective of etiology.
Impact of Darrow’s work of I.V. Therapy

“Effective Replacement of Water and Electrolyte in Patients with diarrhoea should be based on exact knowledge of changes in Composition of Body fluids” – Daniel Darrow, 1949.

Darrow’s work formed the basis for I.V. replacement therapy in infantile diarrhoea that standardized the composition of I.V. Fluids for initial rehydration and for I.V. fluid maintenance until diarrhoea subsides. The policy of “rest to the bowel” (= starving!) and gradual “regrading” with food. This policy took deep root globally including among developing country pediatrician who followed Western Text Books. This is a prescription for disaster in developing countries where childhood malnutrition is very high.

We cite a historical example of early use of sugar / cereal salt solution has been found in old Sanskrit literature in medicine : “Susruta Samhita III, Verse II (1500 BC- Estimated Diarrhoea victims should be “given to drink a profuse quantity of tepid water in which rock salt and molasses have been dissolved or clarified water combined with rice gruel”.

Major Shift from Cholera Treatment Paradigm

Alma Ata Declaration Mortality estimate due to Diarrhoea and Malnutrition in under five children (>5 million/hr globally) Success of ORT among Bangladesh Refugees in a massive outbreak of Diarrhoea/Cholera

Early Documented use of ORT in Cholera : H. N. Chatterjee (1953)

As early as in 1953 Dr. Hemendra Nath Chatterjee documented for the first time the successful use of ORT based on glucose and sodium chloride of a composition closely similar to modern day ORS formulation. In early 50’s Calcutta saw a massive outbreak of cholera and the main Hospitals were overloaded with patients with diarrhoea and dehydration due to cholera (“Control of Vomiting in Cholera and Oral Replacement of Fluid” – Hemendra Nath Chatterjee M. D., The Lancet, Nov 21, 1953). The composition of ORS used by him is given here Control of Vomiting in Cholera and Oral Replacement of Fluid. Hemendra Nath Chatterjee, MD, MS, BA. The Lancet, Nov 21, 1953.

The results are summarized :

- Severity : Mild (Blood Sp. gr. 1.062 or less and good pulse) = 33 patients
- Moderately severe (Blood Sp. gr. 1.062-1.064 = 153 patients
- “of 1093 patients, 33 with mild cholera were tided over to convalescence by the administration of fluid by mouth, and 153 with moderately severe cholera were cured by administration of fluid by mouth and by the rectum, ... a total of 186
- cases (17%) in whom intravenous therapy was unnecessary ..... If full use were made of “avomine” (Promethazine Theoclate) to prevent vomiting many more could be saved from drifting into this advanced stage of dehydration and shock. The proportion treated without intravenous therapy might well be higher than 17%.”

He used promathzine to treat vomiting and glucose salt solution rectally in moderate dehydration. The remarkable features of the study are summarized :

- Composition of ORS used is in acceptable range by present day standard.
- Used an anti-emetic Promethazine.
- Used juice of raw leaf of ‘Coleus aromaticus’ an Indian plant. Antibiotics were not used (not recommended then).
- His work was empirical, no indication on the role of glucose on absorption of sodium.
- He did not do intake/output measurements.

This works was empirical i.e. based on observation and experiments only as the physiological basis was not known then. Further, he used an objective severity indicator i.e. blood specific gravity. This work was largely unnoticed and Hemendra Nath Chatterjee remained an unsung Hero.

After Dr. HN Chatterjee’s very elegant study in 1953 his findings were not put to use by other clinicians nor was it noticed by the clinician scientists who worked on ORT development. It was in late 60’s that new initiatives took place i.e. nearly after 15 years. Of particular interest to me was the marker perfusion study of H.P. Schedl and J. A Clifton in human volunteers published in Nature in 1963 (ten years after Chatterjee’s study in 1953 published in Lancet). This study was conducted by two physicians. They showed that glucose enhances sodium absorption in the small intestine, not only in healthy persons but also in nontropical sprue (Celiac Disease) patients who are known to have altered small intestinal function due to celiac disease. Apart from being a human in-vivo study it also showed evidence that glucose mediated salt absorption is present in a diseased intestine.
Clinician Scientists in two Centres, Johns Hopkins International Center for Medical Research in Calcutta and Cholera Research Laboratory (CRL) in SEATO largely carried out the studies to develop ORT in cholera.

**Proof of Concept**

The main concern of the clinician investigators was whether glucose mediated sodium absorption is retained in actively purging cholera patients (a good model of secretory diarrhea). It may be noted that this mechanism was already shown to be present in humans with celiac disease (Schedl & Clifton, 1963).


- Using gut balance study in a few actively purging cholera he showed:
  
  a) Intragastric infusion of glucose containing salt solution is associated with absorption of salt and water.
  
  b) He suggested, “by incorporation of glucose in an oral solution that one may be able to develop an oral treatment regimen which in the average case might completely eliminate the requirement for intravenous fluids.”
  
  c) His study gave no indication of his awareness of the relevant physiological studies or Schedl & Clifton’s marker perfusion study and hence was empirical.

In 1968 two studies one from Calcutta (Pierce et al.) and one from Dacca (Hirschhorn et al.) confirmed that adding glucose to a salt solution reduces net stool loss present in actively purging cholera patients. Further, Pierce provided evidence for net absorption of both water and electrolytes and Hirschorn measured the net loss of water using intragastric electrolyte solution with and without glucose and measured net loss of water only. Pierce further evaluated the impact of increasing glucose concentration and osmolarity of the solution.

**Documented Clinical Application**

Nalin & colleagues in Dacca carried out a clinical study on actively purging cholera patients (Nalin et al. 1968). This work in principle replicates the work of H. N. Chatterjee in 1953, but this time the team was better equipped with the knowledge of glucose mediated enhanced absorption of sodium in cholera. Nalin and colleagues also measured the intake and output using a cholera cot, a simple and efficient tool for this purpose.

All patients received initial I.V. treatment to correct dehydration. The study showed 80% reduction of I.V. need. Two out of 9 study subjects needed additional I.V. therapy. It is amusing to note both Chatterjee’s and Nalin’s papers were published in Lancet, the first one was ignored but the second one got into the limelight.

In 1970 Cash RA et al. documented the use of ORS in 135 cholera patients using a similar design. They used historical control for comparison.

**Proof of Clinical Efficacy, Randomised Controlled Trial (RCT)**

Basic features of RCT are a) concurrent treatment of study and control groups, b) random allocation (assignment revealed only after the patient is registered in the study), objective outcome measures (note: blinding was not feasible). The study by Sack RB et al. (The use of Oral Replacement Solutions in the treatment of Cholera and Other severe Diarrhoeal Disorders: Bull. World Health Organization, 1970) was the first randomized controlled
trial of ORS in cholera (using sealed envelopes) after initial rehydration by I.V. Fluids.

Composition of ORS was closely similar to WHO ORS (i.e. consensus formula for use in all ages). He used 20 controls and 17 in oral treatment group. One out of 17 required additional I.V. Therapy.

The first RCT in children carried out in children was by ‘Mahalanabis D et. al. (Use of Oral Glucose Electrolyte Solution in the Treatment of Pediatric Cholera – A Controlled Study. Environmental Child Health, 1974). It is the first RCT in children carried out in 1970*. It showed that ORT is effective in children with cholera if dehydration at admission is fully corrected by I.V. Later studies have shown that in non-cholera infantile diarrhoea most patients can be successfully treated without I.V. Therapy.

(* Publication delay was partly due to the section editor (Dr. Jelliffe) of the Journal losing the MS and partly to my getting involved with the massive cholera outbreak among 10 million war refugees from Bangladesh)

**Consensus on ORT in Cholera by 1970s is summarized**:

- Principle of abundant precaution was advocated by the concerned investigators.
- ORT is to be used under medical supervision in fixed facilities.
- ORT should not be promoted as home treatment and ambulatory treatment of diarrhoea.
- Training was emphasized.
- Experts advised extreme caution, and recommended its use under expert supervision in Hospitals.


In 1971, Bangladesh war of independence resulted in a massive exodus into West Bengal, India with an estimated 10 million refugees flowing into camps along the border. A severe cholera epidemic broke out with a reported mortality rate as high as 30%. We from the JHU-ICMRT moved into a camp area in Bongaon with a large inflow of very sick cholera patients.

Camp condition was appalling. I.V. supply was scarce and uncertain. Pushed to the wall, we went ahead with ORT for all. Weighed ingredients of ORS, prepackaged in polythene bags were brought in and made up in a large container. Mothers, relatives, friends, anybody available were mobilized to give ORS to all patients. We had to ration intravenous fluid for the very moribund in shock. Mortality in the ORT camps was down to 3 percent.

Dr. Dhiman Barua, Head of the Bacterial Diseases Unit in WHO visited our camp health centre. He was convinced of its effectiveness and robustness and saw the vast potential of this new tool and began boldly promoting it for treating not only cholera but also childhood diarrhoea. Proponents and researchers went on promoting it and expanding evidence particularly in children. Individuals, groups, non government agencies found a simple means to treat a killer disease in children. Dhiman Barua moved it from within WHO for a global initiative.

But the debate was raging as is evident from this comment in a Lancet editorial : “The challenge is translation and validation”.

Let me comment on Dr. Barua’s role within WHO.

Dhiman Barua got ORS packets manufactured and mobilized UNICEF as a partner. In 1975 Jon Rohde and Robert Northrup published a mortality estimate, an alarming 5 million deaths each year in under five children which was later revised by Mike Merson and John Synder.
I summarized below some events in WHO that Dr. Barua narrated, that preceded the birth of the Global Program:

- In 1971 he saw ORT in action among war refugees and Dr. Barua went into action to promote ORT for cholera and childhood diarrhoea.
- Early on he roped in UNICEF as a partner in ORT production and supply.
- He mobilized support of Sulianti Saroso (Chairperson, 1973 World Health Assembly) for a global control program for diarrhoea.
- An estimate of alarming mortality from diarrhoea in children as stated above was used in every forum to promote an ORT based global program.
- In 1974-75 he organized a successful field trial of ORT in children in the Phillipines and used the results to promote a global program.
- Finally he used his chance meetings with Dr. Mahler, the then Director General, in the basement garage of WHO to convince him and to short circuit the bureaucracy.

The CDD program was born through a resolution in the World Health Assembly in May 1978. The program became fully operational in 1980.

Alma Ata declaration on ‘Health for all by the year 2000 using primary care’ approach helped the process.

So what has been the impact. WHO household surveys, USAID supported Demographic and Health Surveys and Multiple Cluster Indicator Surveys of UNICEF, conducted in 80s and 90s showed hardly any change in morbidity, (3 episodes/child/year in under five children globally). In contrast, global estimates of mortality due to diarrhoea in under five children came down dramatically from 4.6 million in 1980, to 3.1 million in 1990, and 1.8 million in 2000, a 60% decline in deaths due to diarrhoea, mainly in children.

Global Deaths from Diarrhoea: Age 0-4 years

Coming back to the comment in Lancet, that such “vision requires validation”. Promoting ORT, convincing the policy makers leading to a global initiative, and achieving a massive impact on deaths from diarrhea in children more than validated the “visions of ORT’s benefits to the world”.

What made the difference?
formulation would be to: (i) use a combination of organic solutes that are absorbed efficiently and relatively independently of each other e.g., glucose and neutral aminoacids (e.g., glycine, l-alanine and l-glutamine) and (ii) use polymers of organic molecules e.g., glucose polymers like maltodextrins which should exert less osmotic pressure and on hydrolysis are expected to be absorbed at a favourable rate.

**Indicators of Absorption Efficiency**: The indicators of absorption efficiency of ORS used in most studies are, rate of stool output which is usually reported as the first 24 h of stool output per kilogram of body weight, diarrhoea duration and total diarrhoeal stool output per kilogram body weight till cessation of diarrhoea. This last indicator is the composite of stool rate and diarrhoea duration and is a powerful summary measure for evaluation of absorption efficiency of an ORS solution.

**Improved ORS : First Generation Studies : Approaches** :

i) One approach was to add an aminoacid glycine to glucose ORS that followed encouraging results with similar solutions in cholera. Although, the solutions were hyperosmolar it was expected that glucose and glycine with independent absorption mechanism would be absorbed fast and create minimum osmotic problem. Subsequently, aminoacids l-alanine and l-glutamine were used in place of glycine because of their better absorption efficiency.

ii) The second approach was to combine glucose polymers and aminoacids to replace glucose in ORS. Apart from the advantage of using a maltodextrin for its low osmolarity this formulation should have the added advantage of enhanced sodium absorption independently by aminoacids.

iii) The third approach was to replace glucose in ORS by glucose polymers like maltodextrins in larger amounts; they have low iniital osmolarity and can deliver increased amounts of substrate i.e., glucose on hydrolysis. However, effective osmotic forces in the small intestinal lumen will depend on the rates of hydrolysis of polymers and of absorption of glucose.

iv) The fourth approach was to use a cooked cereal powder, mainly rice to replace glucose in ORS. This approach followed the serendipitous finding that use of an ORS containing 50 g/l cooked rice powder in place of glucose was associated with clinically significant reduction in purging rate compared to standard glucose ORS (16). Such a solution contains complex starch and some proteins which on hydrolysis would liberate glucose and some aminoacids. Osmolarity of the solution is low and a larger amount of glucose is delivered in the intestinal lumen on hydrolysis. Any undigested starch is likely to be fermented in the colon to short chain fatty acids which would also stimulate absorption of electrolytes and water.

The results of studies on these improved ORS have been summarized in several overviews and meta-analysis. The findings of the studies are briefly summarized.

**ORS with Added Amino-Acids**: Three actively absorbed neutral aminoacids have been studied. They are, glycine (and its peptide glycyll-glycine), l-alanine and l-glutamine. These were added to glucose based or maltodextrin based ORS. Results of a large number of controlled clinical trials were reviewed.

**Cholera – ORS solutions with added glycine or l-alanine or l-glutamine were substantially more absorption efficient than standard ORS for treatment of cholera; this was so, in spite of the solutions being hyperosmolar (350-430 mosm/l). Patients treated with these formulations had a minimum of 30 per cent reduced purging rate than those treated with standard glucose ORS.**

**Acute Noncholera Diarrhoea – Aminoacid containing ORS formulations were not any more absorption efficient than standard ORS in infants and young children with acute noncholera diarrhoea (largely due to diarrhoeagenic *E. coli* and rotavirus). This lack of efficacy appeared to be due to the solution’s high osmolarity which may have offset the beneficial effect of aminoacid mediated improved absorption. This apparent adverse osmotic effect in infants could be related to the patients’ age or the etiologic agents of diarrhoea or both.**

**Maltodextrin Oral Rehydration Solution**: An ORS with 50 g/l of minimally hydrolyzed maltodextrin in place of glucose (20 g/l) was no more effective than standard ORS in infants and young children with acute noncholera diarrhoea, and yet its osmolarity was low (227 mosm/l) to start with. In one of these clinical trials a substantial proportion of children receiving either standard glucose ORS or maltodextrin ORS had apparent increase in stool output and evidence of temporary glucose malabsorption. This suggests that, at least in some infants and young
children, even 20 g/l of glucose may exceed their absorptive capacity. Maltodextrin ORS was not evaluated in cholera.

To conclude, none of the aminoacid or maltodextrin containing ORS formulations tested so far could be considered a better alternative to standard ORS.

Cereal-based Oral Rehydration Solution: In a study evaluating the scope of using popped rice powder (50 g/l) as a practical alternative to glucose in ORS, clinically significant reduction in purging rate in children with cholera and cholera-like diarrhoea was shown in the group receiving rice-ORS compared to those given standard glucose ORS. Since then many trials compared the efficacy of cereal-based ORS (mostly rice-based) with standard ORS and the results have been reviewed. Early on, rice powder (50 g/l) was either cooked for about 10 min and salts were added in concentration similar to standard WHO ORS or a powder of popped rice (without further cooking) was mixed with the same amount of salts and water. More recently industrially produced packets of precooked rice powder plus salts have also been used. In a limited number of studies other cereals like wheat, maize, sorghum and millet were used and results were similar to those with rice ORS.

A meta-analysis of results of 13 randomized controlled trials (1992) comparing rice-based ORS (50-80 g/l rice powder) with standard glucose-ORS recommended by WHO included 531 adults and 424 children with cholera or cholera-like severe diarrhoea, and 344 infants or young children with acute noncholera diarrhoea. Results of this meta-analysis are summarized.

(i) Cholera patients, both adults and children, treated with rice-ORS had substantially reduced purging rate; in the rice-ORS group stool output was reduced by 34 percent (95% CI: 25% to 43%) compared to glucose ORS; and

(ii) in infants and young children with acute noncholera diarrhoea given rice-ORS 24 h stool output was reduced by 18 per cent (95% CI: 6% to 30%) compared to children given glucose-ORS.

Rice-ORS in severely malnourished children – In two randomized trials in 214 severely malnourished children with acute noncholera diarrhoea rice-ORS was equally effective as glucose-ORS in one and more effective in the other; a trend towards reduced stool output in rice-ORS treated group was reported in one and in the other it was significantly reduced.

A revised meta-analysis of rice-ORS trials in children (9 studies on a total of 1172 children) showed that stool output was only reduced by 7 per cent (95% CI: -3%, 15%) which did not achieve statistical significance. It should be noted that more recent studies in children (n = 828) used a more aggressive feeding regimen which included a cereal (usually rice) based food. A more recent meta-analysis which included an additional 1091 children from 2 recent studies (Faruque ASG and Mahalanabis D, unpublished) i.e., on a total of 2263 children, showed similar results.

Some Conclusions on Rice-Based Oral Rehydration Solutions:

i) Rice-ORS substantially reduces diarrhoea (by a third) in adults and children with cholera:

ii) Efficacy of rise-ORS is at least as good as glucose-ORS in acute non-cholera diarrhoea in children given food (containing cereals) shortly after rehydration; in studies where supervised active frequent feeding was not implemented rice-ORS was shown to be superior to glucose-ORS; however, the effect size was not as large as in cholera; and

iii) Rice-ORS is as effective as glucose ORS in young infants under 6 months of age and in severely malnourished infants and children; use of rice-ORS is not associated with any undesirable side-effects or complications.

Glucose Based Reduced Osmolarity Oral Rehydration Solutions: Concern was expressed about the reported clinically significant glucose malabsorption in a proportion of children treated with standard glucose ORS. It was felt that the concentration of glucose in WHO-ORS may exceed the upper limit of glucose absorption rate in a significant proportion of infants and small children with acute noncholera diarrhoea. Early physiologic experiments also suggested that the upper limit of glucose absorption rate may be good deal lower in infants and small children. Secondly, based on experimental studies in animal models of diarrhoea, mostly cholera toxin induced except for one which also used a rotavirus model in rats, several investigators in recent years have proposed that an oral
rehydration solution made hypoosmolar by reducing both the glucose and sodium concentration may be more absorption efficient. This is based on the observation that water absorption is substantially higher from such solutions and that sodium absorption would be sufficient to meet the needs of infants and children with dehydration due to acute diarrhoea, provided the concentration of sodium is 60 mmol/l or higher. Thirdly, the European Society for Pediatric Gastroenterology and Nutrition recommended an ORS solution for infants and children in developed countries with a sodium concentration of 60 mmol/l and a reduced glucose concentration; however, their major concern was sodium concentration which was felt to be high in WHO-ORS for young infants. Furthermore, in a non-randomized open trial, Rautanen and colleagues reported (1993) reduced diarrhoea frequency and shorter hospital stay with an oral rehydration solution made hypoosmolar by reducing the glucose and sodium concentration. Since then a large number of studies have been undertaken to evaluate glucose ORS formulations made hypoosmolar by reducing the concentration of sodium and glucose. These included two multicentre trials, supported by WHO.

**Reduced Osmolarity Oral Rehydration Solution Trials:** A large number of controlled clinical trials used an ORS formulation in which osmolarity was reduced by lowering the glucose and sodium to 75-90 mmol/L and 60-75 mmol/L respectively with a total osmolarity of 225-245 mmol/L (Table 2).

**TABLE 2:** Composition of reduced osmolarity ORS solutions used in published studies compared to the standard solution

<table>
<thead>
<tr>
<th>Components (mmol/mL)</th>
<th>Reduced osmolarity ORS</th>
<th>Standard ORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A¹</td>
<td>B²</td>
</tr>
<tr>
<td>Glucose</td>
<td>75-90*</td>
<td>111</td>
</tr>
<tr>
<td>Sodium</td>
<td>60-70</td>
<td>50</td>
</tr>
<tr>
<td>Chloride</td>
<td>60-70</td>
<td>40</td>
</tr>
<tr>
<td>Potassium</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Citrate/Bicarbonate</td>
<td>10×</td>
<td>30b</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated osmolarity/L</td>
<td>210-260</td>
<td>251</td>
</tr>
</tbody>
</table>

¹ Used in seven studies including a multi-centre trial  
² Used in one study  
³ Used in 5 studies including the recent multicentre trial by WHO  
* One formulation used sucrose in place of glucose, and another used glucose + l-alanine.

In a WHO/ICDDR, B consultative meeting in Dhaka, Bangladesh in 1994 data from studies conducted with these formulations (including unpublished data provided by the investigators) were reviewed. It was concluded that, reduced osmolarity ORS significantly reduced the stool output and diarrhoea duration when compared to standard ORS in infants and children with non-cholera diarrhoea. Some benefit was also shown in a study in adults with severe disease due to cholera but data was insufficient to reach firm conclusions with regard to the possible risk and benefits of such an ORS in cholera. Given the WHO’s preference for a single reduced osmolarity ORS solution suitable for both adults and children, multicentre trials were initiated following this meeting to evaluate a reduced osmolarity ORS with a glucose and sodium concentrations of 75 mmol/L each and an osmolarity of 245 mosm/L both in adults with cholera and in children with non-cholera diarrhoea. The rationale for this composition was to provide a sodium concentration only modestly less than in standard ORS, which was considered important to treat adults with cholera.

**Reduced Osmolarity ORS in Children:** A recent meta-analysis that included this recent multicentre trial summarized the results of reduced osmolarity ORS trials in children. The results of this systematic review are summarized in Table 2. Reduced osmolarity ORS was more effective than standard WHO-ORS in the first time treatment of children with diarrhoea. It reduced the need for unscheduled intravenous infusion (by 39%), stool output during hydration (by 19%) and the number of patients with vomiting during rehydration (by 29%). There was a trend for increased incidence of hyponatraemia (i.e., serum Na⁺ <130 mmol/L) in the children treated with reduced osmolarity ORS solution which was not statistically significant. All these studies were conducted in children admitted to hospitals with dehydration. Oral rehydration solutions are also used to prevent dehydration both at clinics and at homes and in a recent community-based controlled trial in children reduced osmolarity ORS was as efficacious as standard ORS. Furthermore, nonbreastfed children treated with reduced osmolarity ORS had significantly shorter diarrhoeal episodes.

In a recent consultative meeting convened by WHO and UNICEF in New York in July 2001, all available data (both published and unpublished) on reduced osmolarity ORS trials were reviewed with particular attention to policy implications. In this meeting, data from the recent multicentre trial of reduced osmolarity ORS containing 75 mmol/L sodium and 75 mmol/L glucose in children were
Reduced Osmolarity ORS trials in children: meta-analysis of 15 randomized controlled trials.

also reviewed separately. This study was conducted in 5 countries and enrolled 675 children aged 1-24 months. In contrast to the meta-analysis summarized above, this study did not show any difference in stool output between the two treatment groups. However, as in earlier studies, the need to use unscheduled I.V. fluids was reduced by 40% among the reduced osmolarity ORS group. The incidence of hyponatraemia was similar in the two groups. The comparative data between trials using a reduced osmolarity solution containing 75 mmol/L of sodium and those using 50-70 mmol/L of sodium, were compared by WHO. It shows that, need for unscheduled I.V. therapy and occurrence of vomiting were reduced in children receiving either of these reduced osmolarity ORS solutions compared to standared ORS. Stool output was reduced in children treated with ORS containing ≤ 70 mEq/L sodium but it was not so for the group treated with ORS containing 75 mEq/L sodium.

Reduced Osmolarity ORS in Children with Cholera: A small subgroup of patients enrolled in the recent multicentre study (9%) had culture proven cholera. In this subgroup need for unscheduled I.V. therapy was lower in children treated with reduced osmolarity ORS than in children receiving standard ORS (30% vs. 44%). Stool output at 24 hours was not different between the two treatment groups in children with cholera. However, in the other two studies in whom ORS with ≤ 70 mEq/L of sodium was used, stool output was reduced by 30% in children with cholera.

Comparison of studies of reduced osmolarity ORS solution using a sodium concentration of 60-70 mmol/L with those using a sodium concentration of 75 mmol/L pooled analysis by WHO


Use of Amylase-resistant Starch in Oral Rehydration Solutions: In a controlled clinical trial Ramakrishna and colleagues showed that adding an amylase-resistant starch (50 g/L) to standard glucose ORS markedly increased its absorption efficiency compared to standard ORS in adult cholera. In the experimental group the mean stool output during 12-48 hrs was reduced by 40% and diarrhoea duration by 38%. The starch used was derived from a specific variety of corn and when ingested uncooked, 50 to 70 percent of the starch is not digested in the small intestine and it is fermented and converted to short-chain fatty acids in the colon. As discussed earlier short-chain fatty acids stimulate absorption of salts and water from the colon. Additional studies are required to understand the scope and limits of using amylase-resistant starch in improved ORS.

Concluding Remarks

We may conclude from a series of studies conducted in recent years that, the efficacy of glucose-based ORS for the treatment of children with acute diarrhoea is substantially improved by reducing the sodium to 60-75 mEq/L and glucose to 75-90 mmol/L, and total osmolarity to 215 to 260 mosm/L. The most impressive benefit was the reduced need for unscheduled I.V. Therapy. This finding has implications for healthcare resources such as hospital infrastructure, trained personnel, supplies and logistic. Furthermore, reduced osmolarity ORS with a sodium concentration in the lower range (e.g. 60-70 mmol/L) also reduced the stool output and vomiting during treatment. While reduced osmolarity ORS solutions are also efficacious in children with cholera, the risk of some degree of asymptomatic and transient hyponatremia needs to be
addressed. Similar considerations also apply to adults with cholera.

I would like to see more studies on i) a cereal rice based ORS with a lower sodium concentration, and with (ii) a reduced osmolarity ORS containing amylase-resistant starch.

Appropriate feeding during and after diarrhoea is an important strategy and major global effort was necessary to change the old medical practice starving babies during diarrhoea.

**Feeding During Diarrhoea**

Over the last 20 years a large number of studies have introduced early feeding as part of the standard treatment. Subsequently, a series of studies vindicated this clinical wisdom. This conclusion is based on the observation that food does not interfere with recovery from cholera, that it can be absorbed even during an episode of cholera, and that food may provide substrate for ORT.

Molla showed that children with cholera are able to eat and that the mean caloric intake during the acute phase was 75 calories per kg per 24 h. This increased to 111 calories per kg per 24 h two weeks later. Further, he showed that macronutrients can be absorbed by children during cholera. 70% of the fat intake, 47% of the protein intake, 88% of the carbohydrate intake, and 81% of the calories (mean values) were absorbed during the acute phase of the illness. This increased two weeks later to 90%, 74%, 93% and 91%, respectively. Additionally, trypsin and amylase activities in adult cholera patients during a basal period and after a stimulation by Lund’s test meal is well preserved during the acute phase of the disease.

In a group of young children (1-2 years) with cholera, a nitrogen-balance study during the acute phase showed that a positive nitrogen balance could be promptly achieved with liberal milk feeding even before diarrhoea was controlled, even in clinically severe cases. Finally, in a controlled clinical trial, Dr. Khin Muang U, in Burma, compared a group of severely dehydrated children with cholera served with rice meals along with appropriate fluid therapy (initial I.V. followed by ORT) to a control group, who received no food for 24 h. The group receiving rice meals showed a significant increase in the diarrhea stool output but demonstrated a better weight gain compared to the controls. Recovery was uneventful.

In conclusion, early liberal feeding of cholera patients assists nutritional recovery and is compatible with a rapid and uneventful recovery. The concept of early feeding appropriate for age is complimentary with that of the improved ORS. In both situations, additional substrates are provided early in the illness. In one case, they are provided for their nutritive value; in the other, they are provided to increase absorption of electrolytes and water. It may be that the introduction of appropriate food with the variety of nutrients thereby provided, may in fact, convert the standard ORS into an improved ORS.

**References**


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