

CHAPTER I
INTRODUCTION



1. BACKGROUND

1.1. MAGNITUDE OF DIARRHOEAL PROBLEM

The under-five year children (U-5s) in the 3rd world countries suffer 3-4 diarrhoeal episodes in each year. The UNICEF report of "The State of World's Children 1993" stated that annually approximately 3 millions (m) U-5s die due to diarrhoea. Another 3.5m die from respiratory tract infection (RTI) and 2m from measles. The UNICEF has estimated that most of the diarrhoea related death could be averted by the use of oral rehydration therapy (ORT)¹.

These three diseases are the major cause of U-5s death. Diarrhoea contributes the leading role. It causes dehydration and malnutrition. Malnourished children are prone to more infections specially with RTI and measles. Thereby a vicious cycle develops. When this cycle of events is not broken in time, the eventual result is fatal. The treatment of diarrhoea has two vital objectives:

1. Replacement of water and electrolytes to prevent and to treat dehydration .
2. Adequate dietary therapy to prevent malnutrition².

1.2. ORAL REHYDRATION THERAPY FOR DIARRHOEA:

The ORT has largely replaced intravenous (IV) infusion in the management of dehydrating diarrhoea. Because, ORT is less expensive and easier to administer than IV infusion. Among the ORTs, glucose-oral rehydration salts (G-ORS) is mostly available and well recommended standard treatment for diarrhoea²⁻⁵. Due to logistic constraints, needy people cannot get on easy access to it⁶. And sometimes it causes osmotic diarrhoea due to high osmolarity of glucose (111 mmol/l). Other alternatives like sugar-ORS and sugar-salt solution (SSS) can minimize the logistic constraints and cost yet the problem of osmotic diarrhoea exists⁷⁻¹¹.

1.3. CEREAL BASED ORT (CB-ORT)

Since 1981, CB-ORT have been shown to be an effective alternative to G-ORS¹². There are two categories of CB-ORT. The first category is based on complete formula (CB-ORS), and is prepared with 30-80 g cereal powder and standard salts e.g. Rice-ORS, Wheat-ORS, Maize-ORS, Sorghum-ORS etc. Table 1 shows the composition of G-ORS and CB-ORS. CB-ORS has 4 demerits over G-ORS. These are: 1). Twin packet- cereal and salts are packaged separately, 2). Extra maneuver- to make the solution of CB-ORS, one liter of water is to be added to the cereal, then boiled and after cooling salts are mixed in it, 3). Short shelf life (1-3 weeks) and 4). Costly.

1.3.1. TABLE 1. COMPOSITION OF STANDARD G-ORS AND CB-ORS

PARAMETERS	G-ORS	CB-ORS
CARBOHYDRATE:	20 g. glucose	30-80 g. cereal
STANDARD SALTS:		
NaCl	3.5 g	3.5 g
*NaHCO ₃	2.5 g	2.5 g
KCl	1.5 g	1.5 g

*Substitute with 2.9 g Trisodium citrate

The second one is cereal salt solutions e.g. Rice-salt solution (RSS), Wheat salt solution (WSS), Maize-salt solution (MSS) etc. It is made by mixing and boiling of cereal, salt and water. Both ORTs are called food-based ORT, because they are made from cereal food. Among the cereals, rice based ORT were tested mostly. Table 2 shows the relative merits and demerits of rice and glucose to make ORT¹³.

1.3.2. TABLE 2. COMPARATIVE STATEMENT OF GLUCOSE AND RICE AS A BASE IN ORS SOLUTION

PARAMETERS	GLUCOSE	RICE
AVAILABILITY	++	++++
COST / kg IN Taka*	80	10
PALATABILITY	+++	++++
AMOUNT PER HALF LITER IN g	10	25-40
COOKING	No	Yes
DIGESTION	No	Yes
OSMOLALITY IN mmol/l	111	10
CARRIER	One	two
ENERGY PER HALF LITER IN KCal	40	100-160
STABILITY	++++	+++

*Bangladeshi currency 40 Taka=1 US. \$

NB:1 plus=25 positive score for qualitative evaluation

Rice contains about 80-86% starch. It is a mixture of polyglucose - amylose and amylopectin. It has 7-10% protein. It consists of glycine (30-36 mg/100 g), lysine (30-40 mg/100 g) and leucine and isoleucine (30-40 g/100g rice). Rice is more available, cheap, culturally known for taste, provides energy and needs digestion by gut enzyme. The digestion is optimal to provide sufficient carrier glucose through a long segment of intestine without osmotic drawback of fluid to the gut lumen. Rice liberates another carrier glycine. The osmolarity of rice polymer is 10 times less than glucose¹⁴. Inherently, R-ORS has some safety factors against osmotic diarrhoea due to mixing error¹³. Because the users had to add sufficient water to make a drinkable ORT. Although rice is cheaper than glucose but R-ORS has some drawbacks like twin packet, short shelf life and extra maneuver and cooking. All these contribute more cost to R-ORS than G-ORS. To avoid the problem of needing to boil R-ORS, precooked rice (pop rice) is used and called precooked R-ORS (Pc.R-ORS)¹⁵. But the rice cereal sediments promptly and it's self life is poor while keeping salts and precooked rice in one packet, there by adding more cost to it. Hydrolysed rice (glucose polymers :GP) is also used to make a solution of R-ORS and does not need cooking¹⁶ and is called Pc.R-ORS. Due to higher GP, its osmolarity is higher than R-ORS and Pc.R-ORS (Pop rice) (Table 3.). Therefore, a Pc.R-ORS having low osmolarity and without drawbacks is essential.

1.3.3. TABLE 3. RELATIVE MERITS AND DEMERITS OF DIFFERENT TYPES OF RICE BASED ORS

PARAMETERS	R-ORS	Pc.R-ORS	Pc.R-ORS
TYPE OF RICE	Raw	Pop	Hydrolyse
PACKET	Twin	Twin	Single
EXTRA MANEUVER	Yes	No	No
COOKING	Yes	No	No
SHELF LIFE	Short	Short	Lon
COST	More	More	More
OSMOLARITY	Low	Low	High

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

2. RATIONALE

2.1. Critical Problem of Diarrhoea and ORT:

Diarrhoea of the U-5s is one of the major cause of morbidity and mortality in developing countries. In Bangladesh 13/1000 die in each year^{1,17}. ORT, home fluid and food are recommended for diarrhoea treatment to prevent both dehydration and malnutrition^{2,18-26}. Due to logistic constraints and cost, G-ORS is not accessible^{6,7,27,28}. G-ORS, Sugar-ORS and SSS cannot reduce duration of diarrhoea or enhance early recovery or reduce stool output and sometimes cause osmotic diarrhoea^{29-31,32}.

2.2. Advantages of R-ORS:

More than 60% of world's population consume rice as the staple food. It is cheaper than glucose. Being made from staple cereal, culturally R-ORS is more acceptable³³⁻³⁷. Efficacy of R-ORS was found superior to G-ORS in regards to the reduction of stool output and/or duration of diarrhoea in several studies³⁸⁻⁴⁵. The reduction of stool output was more prominent in cholera than other diarrhoea⁴⁶.

2.3. Disadvantages of R-ORS:

Yet, R-ORS has some drawbacks e.g. twin packet, needs cooking, short shelf life, and costly (4 drawbacks).

2.4. Pc.R-ORS from Pop Rice has no Advantage Over R-ORS:

To avoid cooking procedure, Pc.R-ORS based on pop rice^{15,47} was studied. It does not change osmolarity, can be used by mixing in cold water but adds another problem of earlier sedimentation.

2.5. Pc.R-ORS from GP of Rice has Advantages Over Pc.R-ORS from Pop Rice But has the Disadvantage of High Osmolarity:

Pc.R-ORS from hydrolysed rice^{16,48} does not need cooking, available in single packet, has good shelf life but is very costly. Over all, the efficacy of rice GP is similar or less than glucose due to its high osmolarity^{16,49,50}, because about 56% of rice starch is converted to GP.

2.6. Pc.R-ORS of Low GP has Overcome the Drawbacks:

The department of Chemical Engineering of BUET (Bangladesh University of Engineering and Technology)⁵¹ has developed a Pc.R-ORS which yields low osmolarity due to the conversion of 4-5% rice starch by hydrolysis to GP. It is slightly cream in colour and has a mild fried rice smell. It mitigates the 4 drawbacks of R-ORS (Table 4, 5). It is not yet tested. So it deserves a clinical trial.

2.6.1. TABLE 4. COMPARATIVE STATEMENT OF ORS AVAILABLE IN BANGLADESH FROM DIFFERENT SOURCES

PARAMETERS	G-ORS	R-ORS	Pc.R-ORS
SOURCE	General	ICDDR, B	BUET
PACKET	Single	Twin	Single
FORM OF BASE	Anhydrous	Raw powder	Pre-cooked
AMOUNT OF BASE	10 g. glucose	25 g. rice	25. rice
NaCl	1.75 g.	1.75 g	1.75 g.
NaHCO ₃	1.75 g.	1.25	1.25 g
KCl	0.75	0.75	0.75
WATER	Half Liter	Half Liter	Half Liter
PREPARATION	Instant	Cooking	Instant
COLOR	Colorless	Pale white	Cream
SMELL	No	Cooked rice	Fried rice
TASTE	Sweet-salty	Salty	Salty
SHELF LIFE approx.	2 Years	2-4 Weeks	6-8 months
STABILITY OF SOLUTION IN HOURS	12-18	10-14	10-14
COST IN Taka	3.00	5.00	3.00

2.6.2. TABLE 5. REPARATION AND USE OF ORS SOLUTION FROM DIFFERENT ORS

G-ORS	R-ORS	Pc.R-ORS
Half Liter Water	Half Liter Water	Half Liter Water
1 Packet of G-ORS	1 Packet of R-ORS	1 Packet of Pc.R-ORS
Mix	Mix	Mix
-	*Cook with Stirring	-
-	Till boiling	-
-	Cool and	-
-	Add Salts from	-
-	Another packet	-
-	And mix	-

* 3-4 minutes

2.7. Rice Based Food is Better than G-ORS:

Rice based food formula has been demonstrated better efficacy^{39,52-54} than G-ORS. So, the efficacy of rice based food with G-ORS has importance. But two studies did not observe any difference between G-ORS with feeding and G-ORS without feeding^{44,55}.

2.8. Continuation of Feeding is Recommended with ORT:

ORT and feeding are essential for diarrhoea management. Rice based food has shown a beneficial impact on diarrhoeal outcomes. Therefore, the comparison of efficacy between R-ORS+food and G-ORS+food is important. If G-ORS+food can show the better efficacy, than the use or switch over to R-ORS is not worthwhile. One study⁴⁴ (2x2 factorial design) compared G-ORS, G-ORS+food, R-ORS, R-ORS+food. And observed that food does not potentiate the efficacy of either glucose or rice based ORS in adults with cholera. But R-ORS with or without food substantially reduced the stool output compared to G-ORS with or without food.

The next study⁵⁶ observed that stool reduction in children with cholera during the first 24 hours for R-ORS group was less compared to the G-ORS group. But in next 24 hours, when food was given to both groups, the G-ORS group showed more stool reduction than R-ORS group. The study did

not compare the total stool reduction. Since, the R-ORS group had already substantially reduced stool volume in the first 24 hour and leaving little scope to show stool reduction during the second 24 hours when the G-ORS group showed significant stool reduction following the introduction of food. There is some evidence that more food intake is associated with cereal based ORT^{47,57-59}. These two studies^{44,56} failed to show the comparison of impact of ORS on food intake. Because, they withheld food for 24 hours to see the impact of ORT. Also, both the studies observed the impact of food and ORS on cholera but not on other watery diarrhoea. They used the R-ORS, which has 4 drawbacks. Another study showed the efficacy of Pc.R-ORS+food was better than G-ORS+food⁴⁸. But it used two different types of food for two groups and also introduced food at different stages of treatment. Though it showed Pc.R-ORS was better than G-ORS but the result was not convincing due unequal use of food.

2.9. Continuation of Equal Feeding with Pc.R-ORS (HighGP):

A recent trial¹⁶ studied Pc.R-ORS based on high GP and G-ORS with the early introduction of food on non-cholera watery diarrhoea of children aged 3-18 months. The study found better efficacy of G-ORS+food than Pc.R-ORS+food. It observed comparable efficacy during the initial rehydration phase and identical onset of food

intake. The study used Pc.R-ORS with high osmolarity (56% of rice converted to GP). Therefore, the efficacy at initial rehydration and onset of food intake were comparable with G-ORS. And when food was introduced, Pc.R-ORS showed less efficacy than G-ORS. These findings are different from previous studies^{44, 48, 56}. These three studies observed better efficacy of R-ORS than G-ORS at initial rehydration phase. In this study¹⁶, when food was introduced, the higher stool output, more ORT intake and more duration of diarrhoea were observed due to greater GP load (50 g/l) with food in the Pc.ORS group compared to the G-ORS group (20 g/l) with food. Studies showed that glucose and rice GP were equally digested and absorbed in children with diarrhoea^{49, 50}. In this study¹⁶ the higher load of glucose from high GP probably produced higher osmotic load than the glucose of G-ORS. Consequently reflected the impact of Pc.R-ORS by showing less efficacy than G-ORS. Though the baseline data were comparable, but the study included subjects with history of G-ORS usage.

Still, the impact of ORT with feeding on watery diarrhoea is uncertain. One study said that R-ORS with or without food is better than G-ORS with food in cholera⁴⁴. Another study said that R-ORS is better than G-ORS in the first 24 h. But when food is given, G-ORS is better than R-ORS⁵⁶. But the last study showed Pc.R-ORS with feeding is

less efficacious than G-ORS with feeding in acute watery diarrhoea¹⁶. The meta-analysis⁴⁶ found less stool reduction for children with R-ORS on non-cholera watery diarrhoea than cholera. This issue needs to be addressed whether R-ORS with food has any better impact than G-ORS with food on non-cholera watery diarrhoea of children.

2.10. Testing of Pc.R-ORS of Low GP with Feeding on Non-Cholera of U-5s: Therefore, a clinical trial is essential to determine and compare the efficacy of Pc.R-ORS with low GP +feeding vs. G-ORS+feeding on acute watery diarrhoea of U-5s.



ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

3. LITERATURE REVIEW

3.1. Status of glucose oral rehydration salts (G-ORS):

The origin of glucose-oral rehydration salts (G-ORS) started from the concept of carrier glucose which accelerate the co-transportation of sodium and water from the intestinal lumen to the vascular space⁶⁰⁻⁶². The G-ORS for correct case management of diarrhoea has been recognized world wide as the best currently available intervention to reduce diarrhoeal mortality³⁻⁵. Millions of packets of G-ORS are supplied by the WHO and UNICEF in the developing countries through the control of diarrhoeal disease (CDD) program. They have been vigorously promoted to make G-ORS accessible to the needy population by the year 2000. To attain this goal, these agencies are providing G-ORS packets to 60 developing countries with technical assistance to 14 countries to produce adequate G-ORS. In addition, many pharmaceutical companies and non-government organizations (NGOs) are producing it.

It is understood that, packet G-ORS though effective and desirable is not easily available and accessible to the population at risk. Due to logistic constraints and cost, the supply of it falls far below the total demand. During 1992, the global production of G-ORS reached two-third of it's target production by the year 2000. Also the main

indicators to assess the ORT status are very poor. During 1992, the population with access to ORS was 73% and use rate of ORT was 21%⁶. These figures point out the ineffectiveness of current approaches and activities to promote ORT. Moreover, the users /mothers often do not understand the relation between diarrhoea and dehydration, and their primary concern is to see the diarrhoea stop or 'stool form earlier' while using G-ORS. It is difficult to convince the users to continue it, because it neither reduces the rate of stool loss nor the duration of diarrhoea²⁹⁻³¹. These critical issues probably account for the widespread use of so called 'antidiarrhoeal drugs' and antibiotics⁶³. A survey on household management of diarrhoea in Bangladesh revealed that 43% of diarrhoea cases use indiscriminate drugs⁷.

3.2. ALTERNATIVE ORT: Several alternative ORTs have been tried by scientists to make ORT more available, cheap, accessible, effective and safe.

3.2.1. Glycine based ORS: Being a carrier of sodium, glycine- ORS was tried and found to reduce stool output in diarrhoea and was safe⁶⁴⁻⁶⁶. But the cost has restricted its feasibility.

3.2.2. Sugar-ORS: The use of sugar-ORS (replacing costly glucose with sugar) was studied and found to have comparable

efficacy in terms of rehydration and recovery with G-ORS⁶⁷ in cholera and other severe diarrhoea of adults. A double blind study compared it's efficacy in rotavirus diarrhoea of children³². It was suitable for poor countries⁶⁸ but its short shelf life due to changing color has restricted it's practicability. Sometimes it causes osmotic diarrhoea.

3.2.3. Sugar salt solution (SSS): Early start of diarrhoea treatment at home can reduce the disease burden and mortality from dehydration³. To develop a cheap homemade ORT, the efficacy of sugar (brown sugar) and salt (common salt) solution (SSS) was studied in the treatment of watery diarrhoea of adults⁶⁹. The efficacy of SSS in comparison to G-ORS lead to its promotion at the community level with the training of mothers⁷⁰ and village practitioners⁷¹. At the same time, to make a simple ORT of SSS, several devices were developed e.g. tea spoon, special spoon, 'pinch and scoop'. The CDD program encouraged its use for developing countries. But the chance of mixing error was found to be very high⁸⁻¹¹ and it was abandoned by some countries⁸, though WHO still suggests its use with salt 3g and sugar 18g per liter of water². In rural household condition, this recipe cannot be used due to unavailability of measuring scale. Some countries are now using SSS by 'pinch and scoop' device⁷².

Neither the Sugar-ORS nor the SSS show any demonstrable improvement over G-ORS in reducing stool volume and duration of diarrhoea³⁰⁻³². Therefore, users cannot be fully convinced of the value of continued use of sugar based ORT. The osmolarity of glucose is 111 mmol/l. Both the sugar and glucose based ORT have a problem of high osmolarity to drawback fluids into the lumen of the gut from the vascular space. Also there is chance of mixing errors⁷⁻¹¹, that may give a hypertonic solution leading to more purging.

3.3. STUDIES OF CB-ORT

3.3.1. IMPACT OF CEREAL ON DIARRHOEA:

The first reported effect of rice water (thin fluid from cooked rice: a traditional food preparation from rice approximately contains 5.79 g/dl of ORT solution) on diarrhoea was studied in 1980 at Singapore⁷³. 67 infants were randomly selected (RCT: Randomized Controlled Trial) for rice water treatment and 63 for G-ORS. Both groups were given milk from day 1. All cases recovered by day 5. The rice water group had significantly less stool frequency from day 1 to day 4. The author suggested the prospect of combined rice and standard electrolytes in the treatment of childhood diarrhoea in poor developing countries. (Table 6a)

TABLE 6a. CRITICAL REVIEW OF RICE-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
	1980	1981	1982	1982-83	1982-83
STUDY YEAR:	1980	1981	1982	1982-83	1982-83
Author	Wong	Molla	Patra	Molla	Molla
Country	Singapore	B.desh	India	B.desh	B.desh
Reference	73	12	15	38	38
STUDY DESIGN:	R	R	R	R	R
n/n	67/63	59/65	26/26	84/101	85/72
RICE-BASED ORT rice in g/l	Rice water 5.7	R-ORS 30	PC.R-ORS pop 50	R-ORS 80	R-ORS 80
GLUCOSE-ORS glucose in g/l	G-ORS 20	G-ORS 20	G-ORS 20	G-ORS 20	G-ORS 20
CO-INTERVENTION	Milk	no	-	-	-
BASE LINE COMPARABLE:	yes	yes	yes	yes	yes
age	Infant	adult+child	3-59 mo	<10 yr	>10 yr
sex	both	both	both	both	both
Pre-Study Diarrhoea Time	-	<24 h	27 h	<24 h	<24 h
DEHYDRATION: mild	yes	no	no	no	no
moderate	yes	yes	yes	yes	yes
severe	-	yes	yes	yes	yes
CAUSE:V.cholera	-	yes	yes	yes	yes
E.coli	-	yes	yes	yes	yes
Watery diarrhea	yes	yes	yes	yes	yes
OBSERVATION days	1-5	1-2	1-3	2-3	2-3
CASES EXCLUDED	no	yes	yes	yes	yes
OUTCOMES:					
ORT intake	-	yes	yes	yes	yes
Food intake	-	no	yes	no	no
Frequency of stool	yes	-	no	no	no
Stool output	-	yes	yes	yes	yes
Urine output	-	yes	yes	no	no
Dehydration	yes	-	-	-	-
Duration of diarrhea	-	-	yes	yes	yes
Weight change	-	yes	yes	yes	yes
BLOOD: Serum sp.gr.	-	-	no	-	-
Sodium	no	no	no	no	no
Potassium	no	no	no	no	no
Bicarbonate	no	no	-	-	-
Chloride	no	no	-	-	-
Urea	yes	-	-	-	-
COMPLICATION	no	no	no	no	no
CONCLUSION:R-ORT=G-ORS					
R-ORT better	yes	yes	yes	yes	yes

3.3.2. Clinical Studies of CB-ORT from 1981 to 1993:

1. The second study of CB-ORT was conducted in 1981 at ICDDR,B, hospital, Dhaka, Bangladesh¹². The study selected 126 adults and children with acute diarrhoea due to *V. cholerae* or *E. coli* having moderate to severe dehydration. One group was treated with standard G-ORS and another with R-ORS (30 g/l). The outcomes were measured in the first 24 hours in terms of stool output, ORS solution intake, urine output, serum specific gravity, post hydrolysis sugar content of stool, weight gain and failure of ORT (IV fluid infusion after ORT). The proportion of successfully treated patients were 80% for cholera and 88% for *E. coli* in both age groups. There was no difference in stool output and ORS consumption for adult cholera, but for children with cholera G-ORS consumption was more and stool output was slightly more. It was not clear, how the severe dehydration was corrected?. Did they use any IV for initial dehydration? The study concluded that R-ORS was as safe as that of G-ORS. (Table 6a)

2. The third clinical trial of Pc.R-ORS versus G-ORS was done in 1982 at Calcutta, India¹⁵. Pc.R-ORS was made from pop rice (precooked). This was a RCT with 26 subjects in each group, aged between 3-59 months and admitted with acute watery diarrhoea from *V. cholerae*, *E. coli* and Rotavirus diarrhoea with moderate to severe dehydration. The study was not blinded. One group was treated with G-ORS and another

with Pc.R-ORS (50g/l). The management of initial rehydration was not clear. In the first 24 hours the stool output and ORT use was less in the Pc.R-ORS group than in the G-ORS group. All patients recovered within 72 h. The mean duration of diarrhoea was less and weight gain was more for the Pc.R-ORS group (Table 6a).

3. Between December 1982 and March 1983, during a cholera outbreak, 342 adults and children with moderate and severe dehydration were treated at outpatient department of ICDDR,B³⁸. This was RCT. On admission 75% of patients were moderately dehydrated and 70% cases had cholera. After initial rehydration of severely dehydrated patients, they were treated either by G-ORS or R-ORS (80g/l). The study analyzed the data in two age group. The stool output in the 1st 24 hours was less in adults and children in the R-ORS group and consumption of the R-ORS solution was less than the G-ORS solution. The duration of hospital stay was slightly less for the R-ORS group than the G-ORS group (Table 6a).

4. To know the efficacy of traditional rice food (congee: boiled fermented rice) based ORT, a RCT of rice water, R-ORS and G-ORS was conducted from March 1983 to May 1984 at Bombay, India³⁹. The author recruited 50 infant aged under 6 months with acute watery diarrhoea. The interventions were rice water (rice congee Table 6b), Rice-ORS (rice

TABLE 6b. CRITICAL REVIEW OF CEREAL-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
STUDY YEAR:	1983-84	1983-84	1983-84	1983-84	1985
Author	Mehta	Mehta	Alam	Alam	Mohan
Country	India	India	B.desh	B.desh	India
Reference	39	39	40	40	74
STUDY DESIGN:	R	R	R, block	R, block	R
n/n	50/50	50/50	26/26	26/26	25/25
CEREAL BASED ORT	R-ORS	Rice water	R-ORS	W-ORS	R-ORS
cereal in g/l	congee	congee	50	50	30
GLUCOSE-ORS	G-ORS	G-ORS	G-ORS	G-ORS	G-ORS
glucose in g/l	20	20	20	20	20
CO-INTERVENTION	milk	milk	food	food	-
BASE LINE COMPARABLE:	yes	yes	yes	yes	yes
age	<6 mo	<6 mo	1-8 yr	1-8 yr	3-18 mo
sex	both	both	both	both	both
Pre Study Diarrhoea Time	-	-	<72 h	<72 h	-
DEHYDRATION: mild	yes	yes	no	no	no
moderate	yes	yes	yes	yes	yes
severe	yes	yes	yes	yes	yes
CAUSE: V.cholera	-	-	yes	yes	no
E.coli	-	-	-	-	-
Watery diarrhea	yes	yes	yes	yes	yes
OBSERVATION days	1-5	1-5	3-4	3-4	2-3
CASES EXCLUDED	yes	yes	yes	yes	-
OUTCOMES:					
ORT intake	-	-	yes	yes	yes
Food intake record	-	-	-	-	-
Frequency of stool	yes	yes	-	-	-
Stool output	yes	yes	yes	yes	yes
Urine output	-	-	-	-	yes
Dehydration	yes	yes	yes	yes	yes
Duration of diarrhea	yes	yes	yes	yes	yes
Weight change	yes	yes	-	-	-
BLOOD: Serum sp.gr.	yes	yes	-	-	-
Sodium	yes	yes	-	-	-
Potassium	yes	yes	-	-	-
Bicarbonate	yes	yes	-	-	-
Chloride	yes	yes	-	-	-
Urea	no	no	-	-	-
COMPLICATION	no	no	no	no	no
CONCLUSION: CB-ORT=G-ORS					yes
CB-ORT better	yes	yes	yes	yes	-

congee with standard salt Table 6b) and G-ORS. Congee was used to dilute milk but not the G-ORS. The study concluded the superiority of congee based ORT in reducing stool frequency , stool volume, and increasing weight between admission and recovery and less duration of hospital stay than G-ORS. Congee is a traditional food preparation but not a generally accepted food due to a bad smell. So it's role in the field of ORT is very limited.

5. To explore the possibility of other cereal based ORT, a RCT (block design) with three treatment groups and 26 children aged 1-8 years for each group was conducted between April 1983 to April 1984⁴⁰. The stratification was done on aetiology of diarrhoea (cholera and non-cholera). The interventions were partially hydrolysed (wheat) W-ORS, R-ORS and G-ORS. The consumption of ORS solution and stool output were less in W-ORS and R-ORS than the G-ORS group in the first 24 h with a similar trend in the next two 24 h periods. The duration of diarrhoea was shorter for W-ORS and R-ORS. The study showed the change of stool output for consecutive 3 days. But the study samples were taken from children excluding the under one year age group. The study explored the possibility of alternative cereal (other than rice). But the enzymatic treatment of wheat added more cost and distorted it's physical properties. The starch of wheat was hydrolysed to glucose (3%), maltose (60%) maltotriose (15%)

maltosaccharide (15%) and fructose (2%). With a 26 cases in each group and sub grouped into cholera and non-cholera groups, the authors showed the significant difference between cereal based groups (W-ORS and R-ORS) and G-ORS for stool output and ORS intake on days 1, 2 and 3. Though not significant but almost consistent trends of less stool output and ORT intake were for the R-ORS group as opposed to the W-ORS group. Probably, this was due to the hydrolysis of 95% wheat resulting a high osmolarity of W-ORS. It needs further investigation. (Table 6b).

6. Another RCT with G-ORS and R-ORS was tested on 25 infants (3-18 months) for each group⁷⁴. The non-cholera diarrhoeal outcomes were comparable in both groups in regards to safety, efficacy and acceptability. The study used small amount of rice (30 g rice/l) to make the R-ORS solution and found a equivalent stool output and ORT intake (efficacy) compared to the G-ORS. This finding is consistent with the 1st study of R-ORS¹² which used 30 g rice/l (Table 6b).

7. Bhan et al repeated Pc.R-ORS and explored the possibility of mung bean based ORT. They conducted a RCT with a three treatments design on children between 3 months to 5 years with acute diarrhoea and moderate dehydration⁴⁷. The interventions were Pc.R-ORS (pop rice 50 g/l), Mung bean ORS (60 g/l) and G-ORS (20 g/l). (Table 6c).

TABLE 6c. CRITICAL REVIEW OF CEREAL-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
STUDY YEAR	1986	1987	1988-89	1990	1991
Author	Bhan	El-Maugi	Felipe	Martinez	Pietsching
Country	India	Egypt	Mexico	Mexico	Mexico
Reference	47	41	52	53	54
STUDY DESIGN:	R	R, block	R	R	R
n/n	31/33	30/30	22/22	35/35	70/48
RICE-BASED ORT	R-ORS	R-ORS	Rice	Rice	Rice+Low Na ⁺
rice in g/l	pop 50	50	50	gruel	carrot
GLUCOSE-ORS	G-ORS	G-ORS	G-ORS	G-ORS	G-ORS
glucose in g/l	20	20	20	20	20
CO-INTERVENTION	food	milk	-	no	-
BASE LINE COMPARABLE:	yes	yes	yes	-	yes
age	3-59 mo	4-18 mo	1-8 mo	<5 yr	3-48 mo
sex	both	male	both	both	both
Pre-Study diarrhoea Time	-	-	<17 day	-	-
DEHYDRATION: mild	no	yes	yes	yes	yes
moderate	yes	yes	yes	yes	yes
severe	no	no	no	no	no
CAUSE: V.cholera	-	-	-	-	-
E.coli	-	-	-	-	-
Watery diarrhea	yes	yes	yes	yes	yes
OBSERVATION days	2-3	2-3	1-2	1-3	1-3
CASES EXCLUDED	-	no	-	no	-
OUTCOMES:					
ORT intake	yes	yes	-	-	yes
Food intake record	yes	-	-	-	-
Frequency of stool	yes	yes	-	-	-
Stool output	yes	yes	yes	yes	yes
Urine output	no	-	-	-	-
Dehydration	yes	-	yes	yes	yes
Duration of diarrhea	yes	yes	-	-	-
Weight change	yes	yes	-	-	-
BLOOD: Serum sp.gr.	-	-	-	-	-
Sodium	yes	-	-	-	-
Potassium	yes	-	-	-	-
Bicarbonate	yes	-	-	-	-
Chloride	yes	-	-	-	-
Urea	yes	-	-	-	-
COMPLICATION	no	no	no	no	no
CONCLUSION: CB-ORT=G-ORS					
CB-ORT better	yes	yes	yes	yes	yes

The outcomes were that more serum Na^+ , K^+ , Cl^- , HCO_3^- , glucose achievement and less purging were noticed with Pc.R-ORS than G-ORS and mung bean ORS but not recovery by day 3. Though not significant but the findings were not consistent. Because less purging for the Pc.R-ORS should have a trend of earlier recovery and more purging for the mung bean ORS should have delayed recovery. The intake of semisolid food was significantly more with the Pc.R-ORS. All these contrasting findings suggests another trial with more subjects.

8. A RCT of permuted block design (on age and dehydration) of R-ORS (50g/l) and G-ORS was conducted on 30 cases in each group with formula fed male infants aged between 4-18 months for outcomes of acute diarrhoea⁴¹. The duration of diarrhoea, frequency and volume of stool, ORT intake, vomiting frequency were less and more weight gain were for the R-ORS and were significantly different from the G-ORS. (Table 6c)

9. In Mexico (1988-89), a 3 cells RCT (rice solution, G-ORS by mouth, G-ORS by naso-gastric infusion) was done on total 66 infants aged 1-8 months⁵². The study observed the significant reduction of stool output and dehydration with the rice powder solution compared to the G-ORS. Subsequently another study tried a traditional rice gruel and compared it with G-ORS in a RCT on 70 U-5s having acute watery diarrhoea with mild to moderate dehydration⁵³. The rice solution group

required less time to rehydrate with less stool output. Another study found the similar efficacy with a traditional carrot-rice viscous solution comparing with low (55 mmol/l) sodium and standard sodium (90 mmol/l) G-ORS⁵⁴. The findings of both studies^{53,54} which used traditional rice gruel have encouraged to use the traditional food based fluid for the treatment of children with acute watery diarrhoea (Table 6c).

10. To find out other suitable cereals as a base of ORT, a 7 cells trial on 266 children aged 1-5 years with moderate severe dehydration was conducted between 1984 to 1985 at ICDDR,B⁴². The control cell was G-ORS and study cells were Rice-ORS, Maize-ORS, Wheat-ORS, Millet-ORS, Sorghum-ORS and Potato-ORS. The digestibility of food based ORS was assessed by stool pH, pre and post hydrolysis of glucose content and osmolarity and these findings were comparable with G-ORS. The stool output was significantly less in all food based ORS than G-ORS. (Table 6d).

11. The effectiveness of Wheat-ORS in early treatment of infantile diarrhoea showed a earlier recovery and weight gain compared to the control G-ORS in Ethiopia⁷⁵. A RCT at Nairobi Kenya, with maize based ORS and G-ORS was conducted on acute diarrhoea of children with mild to moderate dehydration and concluded that maize-based ORS was more acceptable and duration of diarrhoea was less with earlier discharge⁷⁶.

TABLE 6d. CRITICAL REVIEW OF RICE-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
STUDY YEAR:	1984-85	1986-87	1992	1985	1986-88
Author	Molla	Kenya	Razafind-	Khin-Mung	Alam
Country	B.desh	Kenya	Madagascar	S.Korea	B.desh
Reference	42	43	45	55	44
STUDY DESIGN:	R	R	R	R	R
n/n	37/42	51/52	82/68	24/24	42/47
RICE-BASED ORT	R-ORS	R-ORS	R-ORS	Rice+G-ORS	Food+G-ORS
rice in g/l	50	50	50	150/feed	normal
GLUCOSE-ORS	G-ORS	G-ORS	G-ORS	G-ORS	G-ORS
glucose in g/l	20	20	20	20	20
CO-INTERVENTION	no	no	food	no	no
BASE LINE COMPARABLE:	yes	yes	yes	yes	yes
age	1-5 yr	4-55 mo	6-36 mo	2-5 yr	15-60 yr
sex	both	male	both	both	both
Pre-Study Diarrhoea Time	<48 h	<48 h	malnourished	<48 h	≤74 h
DEHYDRATION: mild	no	no	yes	-	no
moderate	yes	yes	yes	yes	yes
severe	yes	yes	yes	yes	yes
CAUSE: V.cholera	yes	-	-	yes	yes
E.coli	yes	-	-	no	no
watery diarrhea	yes	yes	yes	yes	yes
OBSERVATION days	3-5	3-5	4-5	1-2	2-3 day
CASES EXCLUDED	yes	yes	yes	-	-
OUTCOMES:					
ORT intake	yes	yes	no	-	no
Food intake	no	no	-	-	-
Frequency of stool	-	-	-	-	-
Stool output	yes	yes	no	no	no
Urine output	-	-	-	-	-
Dehydration	-	yes	no	-	-
Duration of diarrhea	yes	yes	no	no	no
Weight change	yes	yes	yes	yes	-
BLOOD: Serum sp.gr.	yes	yes	-	-	-
Sodium	yes	yes	-	-	-
Potassium	yes	yes	-	-	-
Bicarbonate	yes	yes	-	-	-
Chloride	yes	yes	-	-	-
Urea	-	-	-	-	-
COMPLICATION	no	no	death	no	no
CONCLUSION: R-ORT=G-ORS		yes			yes
R-ORT better	yes	-	yes	yes	-

It has some similarity with traditional 'Uji' porridge, which is used as breakfast, weaning food and diarrhoea treatment. Subsequently another RCT was done with Maize-ORS, Millet-ORS, Sorghum-ORS, Rice-ORS (Table 6d) and G-ORS in 1986-87 at Western Province, Kenya⁴³. The findings were consistent with the previous study⁴². Following this, a RCT of maize-salt solution (MSS: Maize powder 60/l and NaCl 5 g) compared to the G-ORS was conducted on U-5s for the treatment of acute watery diarrhoea⁷⁷. The MSS group showed less ORT intake, stool output and duration of diarrhoea compared to the G-ORS group. The findings have encouraged to conduct a community study of MSS in rural Kenya. Another study of Sorghum-ORS on 6-24 months old infants with watery diarrhoea showed less stool output and less ORS intake compared to the G-ORS⁷⁸.

12. In Madagascar, 150 malnourished children were treated by R-ORS (50g/l) and G-ORS in a RCT⁴⁵. The outcomes in terms of weight gain, and mortality were similar. But the R-ORS reduced the duration of diarrhoea (Table 6d).

13. To evaluate the efficacy of boiled rice with G-ORS on diarrhoea, a RCT on 2-5 years children with diarrhoea of *V. cholerae* was done in 1985⁵⁵. 24 subjects for study group and another 24 for control G-ORS were included. The stool volume and diarrhoeal duration were less for G-ORS group in first 24 h but Wt. gain was more for boiled rice with G-ORS group.

The study did not compare cereal based ORS but showed impact of cereal with G-ORS on diarrhoeal outcomes (Table. 6d).

14. Since, ORT and feeding are essential and recommended for diarrhoea management and also rice based food showed impact on diarrhoeal outcomes. The efficacy of R-ORS+food vs. G-ORS+food has importance. In Bangladesh (1986-88), a 4 cells comparison (G-ORS, G-ORS+food, R-ORS, R-ORS+food) in a RCT on 182 subjects observed that food does not potentiate the efficacy of either glucose or rice based ORS in adults with cholera⁴⁴. But R-ORS with or without food substantially reduced the stool output compared to those of G-ORS with or without food. R-ORS+Food (early introduction of food) group showed better efficacy than G-ORS+food group (Table 6d & 6e). The next study was conducted in Bangladesh and observed the impact of ORT with food on cholera of U-5s⁵⁶. In a RCT with 93 boys, either R-ORS or G-ORS was given in the 1st 24 h, then in the next 24 h period both groups were given normal food and ORT. The study observed that less ORT intake and less stool output were related with the R-ORS group in the 1st 24 h. During the 2nd 24 h period the stool reduction was significantly less with G-ORS+food than R-ORS+food group. But the study did not compare the total stool reduction and total ORT intake. Also the comparison of onset of early food intake related to ORT was not done because food intake was withheld for 24 h. Since, R-ORS group has already (Table 6e)

TABLE 6e. CRITICAL REVIEW OF CEREAL-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
STUDY YEAR	1986-88	1986-88	1986-88	1986-88	1987-88
Author	Alam	Alam	Alam	Molla	Santosham
Country	B.desh	B.desh	B.desh	B.desh	Egypt
Reference	44	44	44	56	48
STUDY DESIGN:	R	R	R	R	R
n/n	46/42	46/47	47/42	47/46	49/50
RICE-BASED ORT	R-ORS	R-ORS	Food+R-ORS	Food+R-ORS	G-ORS+RF
rice in g/l	50	50	50	50	rice food
GLUCOSE-ORS	Food+G-ORS	G-ORS	Food+G-ORS	Food+G-ORS	G-ORS+SF
glucose in g/l	20	20	20	20	20
CO-INTERVENTION	no	food	no	no	no
BASE LINE COMPARABLE:	yes	yes	yes	yes	yes
age	15-60 yr	15-60 yr	15-50 yr	<5 yr	3-18 mo
sex	both	both	both	male	both
Pre-Study Diarrhoea Time	≤24 h	≤24 h	≤24 h	≤24	<7 day
DEHYDRATION: mild	no	no	no	yes	yes
moderate	yes	yes	yes	yes	yes
severe	yes	yes	yes	yes	yes
CAUSE:V.cholera	yes	yes	yes	yes	no
E.coli	no	no	no	no	yes
watery diarrhea	yes	yes	yes	yes	yes
OBSERVATION days	2-3	2-3	2-3	2-3	1-7
CASES EXCLUDED	-	-	-	-	yes
OUTCOMES:					
ORT intake	yes	yes	yes	yes	yes
Food intake	-	-	-	-	no
Frequency of stool	-	-	-	no	-
Stool output	yes	yes	yes	yes	yes
Urine output	no	yes	no	-	yes
Dehydration	-	no	no	-	-
Duration of diarrhea	yes	yes	no	no	no
Weight change	-	-	no	no	no
BLOOD: Serum sp.gr.	-	-	-	-	-
Sodium	-	-	-	-	-
Potassium	-	-	-	-	-
Bicarbonate	-	-	-	-	-
Chloride	-	-	-	-	-
Urea	-	-	-	-	-
COMPLICATION	no	no	no	no	no
CONCLUSION:R-ORT=G-ORS	-	-	-	-	-
R-ORT better	yes	yes	yes	yes	yes

substantially reduced stool volume in the 1st 24 h and leaving little room to show stool reduction on the 2nd 24 h period when G-ORS group showed significant stool reduction following the introduction of food. The study did not report the comparison of combined impact of ORS and food. Because, it withheld food for the 1st 24 h. Also both the studies^{44,56} observed the impact of food and ORS on cholera but not on other watery diarrhoea of children. Both studies used the R-ORS, which is costly and has some drawbacks.

15. In Egypt, (OCT. 87 - May 88), a four cells RCT was done on 200 infants aged between 3 to 18 months old and hospitalized due to acute watery diarrhoea with dehydration⁴⁸. The treatment regimens were: (Table 6e & 6f).

GROUPS	REHYDRATION AND MAINTENANCE PHASE		
	<u>0-4 h</u>	<u>5-24 h</u>	<u>25 h to recover</u>
G-ORS+Soya based Food	G-ORS	G-ORS+SF	G-ORS+SF
G-ORS+Rice based Food	G-ORS	G-ORS+RF	G-ORS+RF
R-ORS+Soya based Food	R-ORS	R-ORS	R-ORS+SF
G-ORS+Precooked Rice	G-ORS	G-ORS+PR	G-ORS+PR

The initial rehydration was done with the G-ORS for 3 groups and one group with the R-ORS. The R-ORS was precooked and instantly dissolved in water (50g/l) but its osmolality was not mentioned. In the maintenance phase the control group was given G-ORS+SF (lactose free Soya based formula, 200 mmol/l) a 2nd group was given G-ORS+RF (rice based formula, also a precooked rice, 175 mmol/l), a 3rd group G-ORS+boiled rice (precooked rice, osmolality not mentioned) and the 4th group

TABLE 6f. CRITICAL REVIEW OF RICE-BASED ORT AND G-ORS

FACTORS	CLINICAL STUDIES				
	1987-88	1987-88	1989	1990	1990-92
STUDY YEAR	1987-88	1987-88	1989	1990	1990-92
Author	Santosham	Shantosham	Daniel	Lifschitz	Fayad
Country	Egypt	Egypt	Peru	Peru	Egypt
Reference	48	48	49	50	16
STUDY DESIGN:	R	R	before	after	before
n/n	49/50	49/50	16/16	8/7	230/230
RICE-BASED ORT	G-ORS+rice	R-ORS+SF	Rice	Rice	R-ORS+fooc
rice in g/l	precooked	50	rice GP	rice GP	rice GP 50
GLUCOSE-ORS	G-ORS+SF	G-ORS+SF	Glucose	Glucose	G-ORS+Food
glucose in g/l	20	20	-	-	20
CO-INTERVENTION	no	no	no	no	no
BASE LINE COMPARABLE:	yes	yes	yes	yes	no
age	3-10 mo	3-18 mo	4-24 mo	2-4 mo	3-18 mo
sex	both	both	both	both	male
Pre Study Diarrhoea Time	<7 day	<7 day	>14 day	-	<7 day
DEHYDRATION: mild	yes	yes	yes	yes	yes
moderate	yes	yes	yes	yes	yes
severe	yes	yes	-	no	yes
CAUSE: V.cholera	no	no	no	-	-
E.coli	yes	yes	no	-	yes
Watery diarrhoea	yes	yes	yes	yes	yes
OBSERVATION days	2-7	2-7	3	3	2-7
CASES EXCLUDED	yes	yes	yes	no	yes
OUTCOMES:					
ORT intake	yes	yes	-	-	no
Food intake	no	no	-	-	no
Frequency of stool	-	-	-	-	-
Stool output	no	yes	-	-	no
Urine output	no	no	-	-	-
Dehydration	-	-	-	-	-
Duration	no	no	-	-	no
Weight change	no	no	-	-	no
BLOOD: Serum sp.gr.	-	-	-	-	-
Sodium	yes	yes	-	-	-
Potassium	-	-	-	-	-
Bicarbonate	-	-	-	-	-
Chloride	-	-	-	-	-
Glucose	-	-	no	no	-
COMPLICATION	no	no	no	no	no
CONCLUSION: Rice GP=Glucose	-	-	yes	yes	no
R-ORT better	yes	yes	-	-	no

R-ORS+ SF. The study concluded that infants who were given the R-ORS had reduced stool output compared to the control group. Feeding with the boiled rice or the rice based formula was as efficacious as the R-ORS alone. The next efficacious was the soya-based lactose free formula. In this study design, the R-ORS was only given at initial rehydration phase in one group but the boiled rice and the rice based formula were given to another 2 groups at maintenance phase. How did the authors conclude the efficacy of three types of rice were comparable while using in different stage of rehydration.

16. A review paper studied 17 comparison from 13 publications on Rice-based ORT⁴⁶. Out of which 3 studies were not published and 2 studies were on Pc.R-ORS (rice GP). The recently developed Pc.R-ORS may not show the efficacy of cereal. Because, the enzymatic or chemical treatment can change a substantial character of starch by breaking down the starch in to GP and glucose⁴⁸. Before using a Pc.R-ORS we had to review its GP proportion or osmolarity. Otherwise we can not expect a desired result of cereals. The study concluded that the rice-based ORT has impact on the reduction of stool volume during the 1st 24 h of cholera patients but not on the non-cholera patients. Also shorter duration of diarrhoea was for the R-ORS on adults and children cholera were shown but the duration of non-cholera was not shown.

3.3.3. ISSUES ABOUT OTHER ASPECTS OF CB-ORT

1. CB-ORT AND FOOD INTAKE: There are some reports about the increase of food intake is associated with rice or cereal based ORT^{47,57-59}. Possibly this may be another cause of better weight gain for R-ORS users.
2. CB-ORT AND STABILITY: The question of stability of CB-ORT solution makes a drawbacks to its application. This is due to fermentation. Molla et al observed that at clinical setup it is stable between 12-18 h in winter and 9-12 h in summer⁵⁸. The current practice of half liter packet ORS in Bangladesh would minimize the risk of fermentation, since half liter solution is expected to be finished earlier.
3. OSMOLARITY, VISCOSITY OF CB ORT: Solution containing 50-80 g of rice have a lower (10 mmol/l) and less variable solution osmolarity⁷⁹⁻⁸¹. With this low concentration more energy can be provided without osmotic diarrhoea. The chance of making hypertonic solution from mixing error are rare due to biochemical safety factors inherent to rice or cereal polymers¹⁴. Hyperosmolar solution containing more than 80 g/l are too thick to drink.

4. ROLE OF FOOD WITH ORT IN DIARRHOEA: Food is a vital part to compensate the nutritional loss of diarrhoea. Which could be attained through integrating ORT and dietary therapy^{18-21,48}. Feeding during diarrhoea promote more rapid mucosal healing, Leading to more rapid recovery from malabsorption. Studies showed that digestion and absorption of starch is significant in infants^{22,23}. Different nutrients are significantly digested and absorbed even in acute phase of diarrhoea^{24,25}. Application of this concept is possible at traditional home environment²⁶. Mothers can use it from learning through practical training⁸².

3.3.4. INSTANT R-ORS: PRECOOKED RICE-ORS (based on rice GP)

The better efficacy and effectiveness of R-ORS have encouraged to develop a Pc.R-ORS that would instantly dissolve in water like G-ORS. The glucose polymer of rice is used to make Pc.R-ORS. It contains D-glucose, short chain and long chain polymers. The proportion of these depends on the process of hydrolysis and chemical treatment.

1. A study used rice GP, corn GP and glucose to test the absorption on 16 chronic diarrhoeal infants⁴⁹. The rice GP contained about 56% of glucose and short chain polymers. After 1 h, the serum glucose was higher for glucose and rice GP groups than corn GP group. To make Pc.R-ORS, the quantity of GP in rice is critical. Increasing the proportion of GP in rice, the efficacy of Pc.R-ORS would be closer or similar to

G-ORS. Because the polymers are promptly digested by intestinal enzymes, giving a higher amount of glucose and osmotic load, which may be higher than G-ORS. (Table 6f)

2. To complement cow milk based diet, carbon 13 enriched rice cereal was developed and used for the nutritional management of infants with acute diarrhoea⁵⁰. The before after (pilot study on the availability of ^{13}C rice) study assessed the digestion and absorption of it in 8 infants and found that in 7 children the precooked rice is well absorbed both during diarrhoea and normal period. But the study did not compare it with glucose. (Table 6f)

3. Between Aug. 1990 to Apr. 1992 in Cairo, Egypt, a RCT was conducted. 230 boys aged 3-18 months with acute watery diarrhoea were treated with Pc.R-ORS and G-ORS for 7 days¹⁶. Both groups were equally fed with rice and mixed vegetables (weaning food). The authors concluded that the G-ORS group had less stool output and ORT intake compared to the Pc.R-ORS group. Both group had similar weight gain. The base line comparable. But during the pre study period G-ORS were consumed by both groups. Though not significant, control group have taken more. Therefore, the inception cohorts were not unique. Because, the intervention started with Pc.R-ORS and G-ORS. The study did not mention the proportion of GP in Pc.R-ORS, or its osmolality. Probably the study used Pc.R-ORS

having high content of GP in rice. As a result the Pc.ORS had more stool output than G-ORS and average time of onset of feeding was identical. The same study group did a previous study with the precooked rice⁴⁸ and the R-ORS (both based on rice GP) and observed better efficacy of both compared to the G-ORS. Unless we know the details of this Pc.R-ORS, the result of their study is not convincing. Overall, the sample size was calculated on 20% difference of total stool output but the fecal outputs were shown separately in rehydration and in maintenance phase. (Table 6f).

4. The review paper⁴⁶ has mentioned two recent unpublished Pc.R-ORS studies. The authors are Mochtar, et al and Guiraldes, et al. Through 'MEDLINE' computer search up to 1993, There is no publication indexed against their name with 'precook' or 'Rice-ORS'. Two commercial companies 'Galactina' in Switzerland and 'Hamdord' in Pakistan have developed Pc.R-ORS. The process of enzymatic treatment put more cost with a added problem of osmolarity change. These products are under trial stage.

Between 1981 to 1993 several clinical studies were conducted with cereal based ORT. But the rice-based studies got maximum priority and mostly done. These studies observed mainly the reduction of stool volume and reduction of duration of diarrhoea. The two variables are directly

correlated. Therefore, when there is a reduction of stool output on the R-ORS, there is a possibility of reduction of duration of diarrhoea. Even several studies only used cereal or rice and observed significant impact on stool reduction^{39,52-54}. This is a key issue whether the user/mothers can perceive the same effect, while using the R-ORS with the onset of diarrhoea at home. If possible, then the use of it would likely be increased at community level.

3.3.5. CEREAL BASED ORT STUDIES AT COMMUNITY

1. The encouraging results of clinical studies^{12,15} led to a feasibility study of rice salt solution and observed that rural mothers of Bangladesh can prepare a safe RSS³³ (Table 6g). This was a descriptive study to provided training to mothers with the use of household rice powder and salts to treat diarrhoea at community. The drawback of this study was that it did not compare RSS with SSS or G-ORS. Another community study observed the better effectiveness of RSS³⁴.

2. Following this, a 3 cells community study for 2 years (1983 to 1985) with R-ORS (80 g/l), G-ORS and control, observed the effectiveness. The use rate of R-ORS was more than G-ORS. The decrease of diarrhoeal duration and reduction of chronic diarrhoea was associated with the R-ORS users^{35,36}. The study used twin packet of R-ORS, which had shorter shelf life and needed cooking (Table 6g).

TABLE 6g. CRITICAL REVIEW OF CEREAL BASED ORT AND G-ORS

<u>FACTORS</u>	<u>COMMUNITY STUDIES</u>				
STUDY YEAR	1983	1983-85	1986-87	1987-89	1991
Author	Rahman	Bari A	Rahman	Kenya PR	Bari A
Country	B.desh	B.desh	B.desh	Kenya	Pakistan
Reference	33	35	37	83	59
STUDY PERIOD	4 mo	2 yr	1 yr	18 mo	8 mo
STUDY DESIGN:	Descriptive	Prospect Cohort	Prospect Cohort	Prospect Cohort	Randomized prospect
Objective	Feasibility	Effective	Cost-Eff	Effective	Effective
Diarrhea episodes:n/n	945/0	2399/2405	486/459	2500/3078	183/183
CEREAL-BASED ORT	RSS	R-ORS	R-ORS	MSS	WSS
cereal in g/l	2 fists	80	80	60	2 fists
GLUCOSE-ORS	-	G-ORS	G-ORS	G-ORS	G-ORS
glucose in g/l	-	20	20	20	20
CO-INTERVENTION	feeding	feeding	Feeding	Feeding	Feeding
BASE LINE COMPARABLE:	-	yes	yes	yes	yes
age	All	U-5s	U-5s	U-5s	6-59
sex	both	both	both	both	both
Pre-Study Diarrhoea Time	-	-	-	=	<4 day
DEHYDRATION: no	yes	yes	yes	yes	yes
some	yes	yes	yes	yes	yes
severe	yes	yes	yes	yes	no
CAUSE: Watery diarrhea	yes	yes	yes	yes	yes
Bloody diarrhea	yes	no	no	yes	no
OBSERVATION days	1-14	1-30	1-14	1-30	1-10
CASES EXCLUDED	no	yes	yes	yes	yes
OUTCOMES:					
ORT Use	yes	yes	yes	yes	yes
Food intake	-	-	-	-	yes
Consistency of Stool	-	yes	yes	yes	yes
Frequency of stool	-	yes	yes	yes	yes
Dehydration	-	yes	yes	yes	yes
Duration of diarrhea	-	yes	no	yes	yes
Recovery	yes	yes	yes	yes	yes
Weight change	-	yes	-	yes	yes
ORT : Sodium	yes	yes	-	yes	yes
Potassium	-	yes	-	yes	yes
Bicarbonate	-	yes	-	yes	yes
Chloride	-	yes	-	yes	yes
Glucose	yes	yes	-	yes	yes
COMPLICATION	no	no	no	no	no
CONCLUSION:CB-ORT	Feasible	Better	Not better	Better	Better

3. Subsequently a cost-effectiveness study of R-ORS vs. G-ORS in the perspective of study administration was conducted in 1986-87³⁷. It was found that R-ORS was less cost-effective than G-ORS. The study perspective was wrongly identified. It was to be users perspective. However, R-ORS was not promoted any more for community use. (Table 6g).

4. Another community study was conducted in Western Kenya with Maize-salt solution (1987-89). The study concluded that rural Kenyan mothers can make a safe MSS for home management of diarrhoea. In this study the use of MSS was more than G-ORS⁸³. Following this study, the Kenyan Government is now planning to incorporate MSS in its CDD program (Table 6g).

5. A home clinical trial among Afghan refugee children repeated the superiority of wheat salt solution over G-ORS⁵⁹. In this study, use rate of the WSS was significantly more (84%) than the G-ORS (74%). And failure of the WSS was significantly less (8%) than the G-ORS (29%). Also mothers preferred the WSS to use in Afghanistan, where the CDD program already stopped its activities in 1992. (Table 6g). The health personnel were not rotated between two areas due to social restriction. Another recent operational study in the same community determined best health workers, users, media of approach to users and method of training to treat diarrhoea with WSS⁸⁴.

3.3.6. SUMMARY FINDINGS FROM RICE BASED ORT STUDIES

Total 22 clinical studies on Rice-based ORT are reviewed and found 29 comparisons with G-ORS (Table 6a-6f). Studies with only rice showed better efficacy of the rice compared to the G-ORS^{73,39,52,53,54}. Studies with the R-ORS^{12,38-45,74} or the Pc.R-ORS (pop rice)^{15,47} with or without co-intervention of feeding observed mostly better efficacy of the R-ORS compared to the G-ORS. Studies with early introduction of food found better efficacy of R-ORS than G-ORS^{44,48,55}. But studies introduced food following the 1st 24 h found better efficacy in the 1st 24 h for the R-ORS and better efficacy in the next 24 h for the G-ORS⁵⁶. Only one study with food+G-ORS showed equal efficacy in comparison to G-ORS⁴⁴. Another 2 studies showed that the digestion and absorption of rice GP and glucose are comparable^{49,50}. And last clinical study observed less efficacy of the rice GP based ORS (Pc.R-ORS) compared to the G-ORS¹⁶ with early introduction of food. Most of the clinical comparisons showed better or equal efficacy of rice based ORT. But it has drawbacks e.g. twin packet, short shelf life and needs cooking. It is also not a cost-effective ORS. The Pc.R-ORS (pop rice) does not need cooking but sediments promptly. Due to these reasons it is not practicable in field condition. The Pc.R-ORS based on rice GP (56%)^{16,49,50} gives an instant solution and without drawbacks except cost showed similar or less efficacy in comparison to G-ORS due to its high rice GP and osmolarity.

3.3.6. TABLE 6h. SUMMARY OF STUDIES OF RICE-ORT AND G-ORS

(Efficacy: Yes, Equal and No)				
Rice-ORT Efficacy	Rice-ORT Efficacy	Rice-ORT Efficacy	Rice-ORT Efficacy	Rice-ORT Efficacy
Rice yes	Rice yes	Rice yes	Rice yes	Rice+Low Na+ yes
R-ORS yes	R-ORS yes	R-ORS yes	R-ORS yes	R-ORS yes
R-ORS yes	R-ORS yes	R-ORS yes	R-ORS yes	R-ORS equal
R-ORS equal	Pc.R-ORS yes	Pc.R-ORS yes	Rice+G-ORS yes	Food+G-ORS equal
R-ORS yes	Food+R-ORS yes	Food+R-ORS yes	G-ORS+RF yes	G-ORS+Rice yes
R-ORS+SF yes	Rice GP equal	Rice GP equal	Pc.R-ORS+food no	-
RSS Yes	R-ORS yes	R-ORS no	-	-

Still, there exist a critical issue to find out a low cost ORS having low osmolarity, better efficacy and without any drawbacks. The research and development working group of WHO have given importance and priority in research on low osmolar ORS for case management in health facilities⁶.

Total 8 clinical studies on other cereals are reviewed and found 15 comparisons. All these observed better efficacy of cereal based ORT than G-ORS^{40,42,43,47,75-78}.

Total 6 community studies^{33-35,37,59,83} were observed better effectiveness of CB-ORT including 4 R-ORS studies. One study found that R-ORS is less cost-effective³⁷ (Table 6g).

3.4. THE STATE OF DIARRHOEA AND ORT IN BANGLADESH

Diarrhoeal diseases are still a major cause of morbidity and mortality of U-5s in Bangladesh. Approximately the U-5 age group has 4 episodes in each year. About one third of all death in U-5s are associated with diarrhoea. In 1990, about 260,000 died due to diarrhoea. The childhood diarrhoeal mortality is 13 /1000 children¹⁷. The ICDDR,B (International Center for Diarrhoeal Diseases Research, Bangladesh) report showed that death associated with acute watery diarrhoea is 19%, bloody dysentery 18% and chronic diarrhoea in all diarrhoeal death⁸⁵.

Watery diarrhoea is endemic throughout the year with seasonal peak in pre-monsoon (March-June) and post-monsoon (September-November). The outbreak of rotavirus diarrhoea of U-5s occur in winter (December-February). The table 4. shows some major diarrhoeal diseases epidemics which were experienced in Bangladesh⁸⁵. The geo-climatic and poor socio-economic condition have a profound impact in the prevalence of diarrhoeal diseases in Bangladesh. In addition the gradual deteriorating water and sanitation aggravates the problem of diarrhoea.

3.4.1. TABLE 7. EPIDEMICS OF DIARRHOEAL DISEASES IN BANGLADESH 1974-91

TYPE OF EPIDEMIC	LOCATION	PREDISPOSING FACTOR	YEAR
Cholera and Shigellosis	North & South Bengal	Flood & Food shortage	72-74
Watery diarrhoea	Barisal	Classical strain	82-82
Shigellosis	North Bengal	Drought	84-85
Watery diarrhoea	Sandip & Urirchar	Cyclone	85
Watery diarrhoea	Urirchar	Flood	87
Watery diarrhoea	Country wide	Flood	88
Watery diarrhoea	South-east	Cyclone	91

With UNICEF assistance, the national oral rehydration program (NORP) started G-ORS production in 1979. Now under national CDD, it produces 30m packets per year. In 1983 the NCDD program started functioning²⁷. The health facility survey of NCDD program reported that 3% of diarrhoea cases are correctly assessed, 4% correctly rehydrated, 1% users can give correct home treatment of ORT and dietary therapy²⁸. The household survey revealed that 93% of people are aware of G-ORS packets, 28% use ORT (G-ORS and SSS), 38% can prepare correct ORT and 43% use indiscriminate antibiotics⁷. The high awareness and low use trend of ORT indicates the low supply of G-ORS and ineffectiveness of both G-ORS and SSS.

Therefore, a suitable ORT is essential with better efficacy. It is estimated that currently only for U-5s diarrhoea episodes, Bangladesh needs 310m of G-ORS packet (19.3m U-5s x 4 diarrhoea episodes per year x 4 G-ORS packet per episode). At the same time, the overall production of G-ORS is hardly 100m i.e. one third of national requirement²⁷. The requirement of over-five population is not yet estimated. Moreover, the ORS requirement will recur every year and country needs importing of glucose with valuable foreign currency. There is a limitation for United Nations and international agencies to fulfill the demands to certain extent. In addition, the recent world wide economic constraints might have impact on these agencies to curtail or limit their efforts. Already 4 countries have been dropped from CDD program in 1992 due to political instability or civil war⁶. Therefore, a self sufficiency should be encouraged to meet the huge demand of ORT.

3.5. PROMOTION OF PC.R-ORS IN BANGLADESH

Since 1986, the ICDDR,B Dhaka hospital has been rendering routine services to the diarrhoea patients mostly by R-ORS⁸⁶. Recently, this center has started optional provision of R-ORS packet for diarrhoea patients on payment to use at home, We can easily identify two major issues regarding ICDDR,B policy:

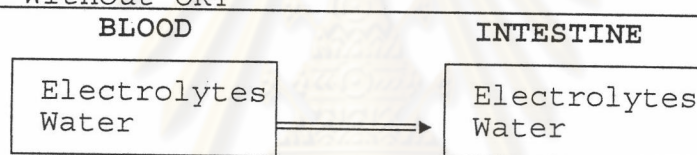
1. If R-ORS is not better than G-ORS, ICDDR,B is not suppose to use it and
2. If users do not perceive the usefulness of R-ORS, Why do they demand it? and why ICDDR,B is obliged to provide it?

At this stage it is clear that R-ORS is feasible at clinical level and there is a demand at community level. Still , there remains (Table 2, page 4) some drawbacks of R-ORS. It is made from raw rice powder, packed in one packet and standard salts in another packet (twin packet). It's shelf life is about 1-3 weeks, needs certain cooking maneuver and costly. In 1993, the UNICEF Dhaka, tried to import Pc.R-ORS from Galactina Co. Geneva for testing. But Bangladesh Government did not give import permit due to its high cost. In 1992, a Pc.R-ORS having low GP has been developed by the Bangladesh University of Engineering and Technology (BUET)⁵¹. Which mitigates the demerits of R-ORS. It instantly mixed in water like G-ORS, shelf life 6-8 months and cheaper. Due to the technical process there is some breakdown (4-5%) of starch to short chain GP, glucose and fructose. Table 5 & 6 show some information about of G-ORS and R-ORS and Pc.R-ORS available in Bangladesh.

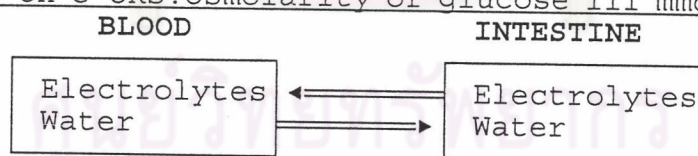
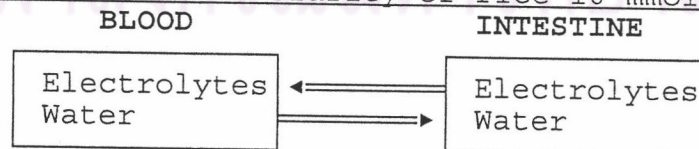
Therefore, a clinical trial is needed to determine it's efficacy to treat acute watery diarrhoea of U-5s in comparison to G-ORS with feeding encouragement to each.

4. CONCEPTUAL FRAMEWORK

4.1. FIGURE 1. ELECTROLYTES AND WATER TRANSPORT THROUGH THE INTESTINE DURING NORMAL & DIARRHOEA PERIOD: IMPACT OF PRECOOKED RICE-ORS AND GLUCOSE-ORS

NORMALDIARRHOEA: Without ORT

CLINICAL ASSESSMENT:	Dehydration Weight loss Urine output decrease Loss of appetite	Stool consistency loose Stool volume increases Stool frequency increases Vomiting
----------------------	---	--

DIARRHOEA: On G-ORS: Osmolarity of glucose 111 mmol/l & 1 carrierDIARRHOEA: On R-ORS: Osmolarity of rice 10 mmol/l & 2 carriers

4.2. DIARRHOEA AND IMPACT OF G-ORS AND R-ORS;

In R-ORS, rice polymers exert 10 mmol/l and provide two carriers to transport electrolytes and water from the gut to the blood without osmotic penalty. Therefore, stool output and stool frequency are reduced with earlier appearance of formed stool. So there is shorter duration of diarrhoea or earlier recovery from diarrhoea. On R-ORS, patients pass less stool, so they consume less ORT. Also the replacement of salts and water results in earlier rehydration and weight gain. Food prevents malnutrition, the patients with diarrhoea can digest and absorb food. So food is given to diarrhoea patient as soon as possible.

4.3. Primary Objective

To determine the efficacy of G-ORS and Pc.R-ORS on acute watery diarrhoea for primary outcomes, we should first consider the definition of diarrhoea. Diarrhoea means passing of loose stool (liquid or watery). According to the WHO, passing of 3 or more loose stool per 24 hours is considered as diarrhoea. Therefore, the consistency and the frequency of stool are important features. Frequent passing of formed stool cannot be considered as diarrhoea. Children on breast milk sometimes pass loose stool (pasty stool) is also not

diarrhoea. In most societies mother's reporting of diarrhoea provides a useful working definition². To determine the efficacy of ORT on non-cholera acute watery diarrhoea, the volume of stool cannot be considered as primary outcome. Because, in non-cholera acute watery diarrhoea the stool reduction is about 18% on R-ORS compared to G-ORS in 1st 24 h. Though significant, this amount of reduction is not clinically significant⁴⁶. Also stool frequency cannot be considered as a primary outcome because, one or two loose motions of large volume are sufficient to cause dehydration. Only the stool consistency of appearance of a formed stool is considered as the primary outcome. But, sometimes a loose stool may reappear following a formed stool. Also, sometimes a patient does not pass any stool for several hours following a loose motion.

Some of the R-ORS studies compared the efficacy by duration of diarrhoea on ORT i.e hospital stay. They did not include the pre admission diarrhoea period to estimate the total duration of diarrhoea. This variable was treated as a baseline variable for comparability. Two studies determined the efficacy of ORT by recovery^{16,35}. They confirmed the duration of diarrhoea on ORT by using time to recovery (log-rank test). So, a recovery of a diarrhoea (from the onset of diarrhoea to the ending of

diarrhoea) and duration of diarrhoea (from the onset of ORT to the ending of diarrhoea) are the same outcome of a diarrhoea if pre admission diarrhoea period is comparable. This study includes acute diarrhoeal subjects with short pre admission diarrhoea period (24-96 h). So, taking the primary outcome as recovery is feasible. The recovery of diarrhoea is defined from the appearance of a formed stool or no stool for 16 hours^{16,44,56} and is confirmed by 0-2 formed stools in the next 24 h. At ICDDR,B hospital, more than 90% of diarrhoea cases have usually recovered by day 3 with the use of R-ORS and feeding⁸⁶. Therefore, a recovery by day 3 to compare the efficacy of Pc.R-ORS and G-ORS can be considered as primary objective.



ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

5. OPERATIONAL DEFINITION

Diarrhoea: Mother's reporting of passing of 3 or more loose stool in the last 24 hours by her child is considered as diarrhoea.

End result: To determine the primary and secondary outcomes of objective, the diarrhoea subjects will be followed-up up to 72 hours. And during this period diarrhoea recover, failure of ORT and drop-out will observed according to definition.

Recovery of Diarrhoea: Appearance of formed stool and confirmed by 0-2 formed stool in the next 24 hours or passing no stool for 16 hours following the onset of ORT.

Failure of ORT: Diarrhoea continues more than 3 days, development of severe dehydration or complications such as oedema, distension of abdomen, IV infusion due to persistent vomiting, persistent diarrhoea, acidosis, anuria for 24 hours and death related to ORT (death from the severe dehydration and/or complications following ORT), non-compliance and non-cooperation/withdrawl from study (not satisfied with treatment/demanding other medication with ORT).

Drop-out: Causes not related to ORT or study procedure.

6. RESEARCH QUESTION

Primary Research Question:

While managing Bangladeshi children aged 4-59 months with non-cholera acute watery diarrhoea by encouraging feeding and ORT compliance at clinical setup:

Is Pc.R-ORS based on low rice GP or standard G-ORS efficacious in increasing recovery by day three in comparison to each other?

Secondary Research Question:

While managing Bangladeshi children aged 4-59 months with non-cholera acute watery diarrhoea by encouraging feeding and ORT compliance and clinical evaluation per 24 hours over a period of 3 days:

Is Pc.R-ORS or G-ORS efficacious in terms of less stool output, more urine output, less vomitus, earlier rehydration, less ORT intake, earlier food intake, more food intake, less duration of diarrhoea and more weight gain in comparison to each other?

7. OBJECTIVES

The objectives of this study are to determine and to compare the efficacy within 3 days of onset of Pc.R-ORS and G-ORS with encouraging of early feeding for 4-59 months old children with acute watery diarrhoea in terms of:

PRIMARY OBJECTIVE:

1. Recovery from diarrhoea within 3 days of onset of ORT.

SECONDARY OBJECTIVE:

2. Stool output /24 h.
3. Urine output /24 h.
4. Vomitus /24 h.
5. ORT intake /24 h.
6. Onset of food intake following onset of ORT.
7. Food intake /24 h.
8. Clinical dehydration status as none, some and severe /24 h.
9. Weight change /24 h.
10. Duration of diarrhoea from onset of ORT to end result.

8. HYPOTHESES

H_0 : Pc.R-ORS = G-ORS

H_a : Pc.R-ORS > G-ORS or Pc.R-ORS < G-ORS

8.1. Null Hypothesis:

Children aged 4-59 months with non-cholera acute watery diarrhoea will be admitted with a comparable baseline. They will be stratified on age and dehydration status and will be randomly allocated to receive either Pc.R-ORS or standard G-ORS. Both groups will be encouraged for early feeding and will be observed over a period of 3 days at clinical setup. The efficacy of both ORT in terms of recovery, stool output, urine output, vomitus, dehydration, ORT intake, food intake, duration of diarrhoea and weight gain would be comparable.

8.2. Alternative Hypothesis:

Under the identical condition (as in null hypothesis) the efficacy of either Pc.R-ORS or G-ORS in terms of more recovery by day 3, less Stool output, more urine output, less vomitus, less dehydration, less ORT intake, earlier food intake, more food intake, less duration of diarrhoea and more weight gain would be significantly better.