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SECTION I - RESEARCH PROTOCOL

1) Title: Sucrose vs Glucose Electrolyte Oral Solution - In the Diarrhea of Adults

2) Principal Investigator: Dr S. Islam

3) Starting Date: September 1977

4) Completion Date: July 1978

5) Total Direct Cost: $18,308

6) Abstract Summary: (250 words or less)

We plan a double blind trial to compare the effectiveness of an oral glucose electrolyte solution (WHO formula) with sucrose electrolyte solution in the hydration of adults with cholera, E.coli and other severe watery diarrheal diseases in Bangladesh. Approximately 150 patients with watery diarrheal diseases, with ages between 16 years and 50 years will be admitted into the study. The primary determinant of failure of a treatment will be the need to begin (or resume) I.V. hydration; however, other factors such as absorption of sugars and patient's acceptance of therapy will also be examined.

7) Reviews:

a) Research Involving Human Subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective: To help eliminate morbidity and mortality resulting from diarrheal disease by developing effective economical oral hydration fluid.

2. Background: The complications and mortality resulting from syndromes of watery diarrhea are almost exclusively limited to those of dehydration. The primary therapy therefore in the watery diarrhea syndromes is that of rehydration and maintenance hydration. In severe diarrheal states this can only be accomplished with intravenous fluids; however, most diarrheal episodes can be managed successfully with oral therapy. Documentation of the effectiveness of oral GE solution has been established in Calcutta, Dacca as well as in the United States, in both cholera and non-cholera diarrhea.

The rationale for using an oral electrolyte-solution is as follows. In cholera and E. coli diarrhea the diarrhea results from an activation of cyclic AMP with resulting massive outpouring of fluids and electrolytes from the mucosal cells of the small bowel. Absorption however, remains normal throughout the small intestine.

There are three primary modalities through which electrolyte and water are absorbed by the small intestine:

1) The sodium pump system which carries water along with sodium.

2) Passive absorption of water.

3) Glucose facilitated absorption.

It is this glucose facilitated absorption which is utilized in the oral glucose-electrolyte rehydration therapy.

The advantages of oral solution for the treatment of watery diarrheal syndromes are several:

1) The volume of sterile intravenous solution is greatly decrea. ed. This is of very particular importance in the areas where intravenous solutions are limited either by facilities or by economic considerations.

2) Intravenous solutions may be avoided altogether in some patients thus avoiding complications of intravenous infusions.

3) This may be a very practical form of therapy in which hydration can be carried out in the home without the use of hospitals and it is especially useful in epidemics of watery diarrhea where logictics prohibits wide se of intravenous solutions.

Most of the experience with oral solution have been with a glucose based solution. In many areas glucose is not available, and when

available is not inexpensive. Sucrose offers a reasonable alternative to glucose since the sucrose could be broken down by disaccharidase in the gut releasing glucose and fructose which would then be utilized in the glucose facilitated transport. From a practical standpoint, sucrose is always available and cheaper than glucose hence would have definate advantages in developing countries. Against the use of sucrose in oral solutions is the fact that disaccharidase is often depressed in acute diarrheal disease, hence the sucrose may not be hydrolyzed adequately. Hence a controversy continues as to the potential efficacy of a sucrose electrolyte solution.

Studies done at CRL unfortunately have not answered the question as to the relative efficacy of the two solutions. On the basis of a few patients Dr. Nalin feels that sucrose solution is associated with an unacceptably high failure rate. Drs. Palmer and Koster carried out a double blind trial in 1974 and interpreted their results as showing no difference between the two solutions. Failures on oral fluid were however found whenever the purging rate was very high. From Calcutta Dr. Mahalanabis recently reported a study in children comparing the two solutions and felt that the two solutions were equal. The numbers of patients studied however was small, the purging rates were low and in most cases the etiologies were unknown. Hence the studies done at CRL and elsewhere have failed to answer the controversial question concerning sucrose oral solution.

3. Rationale: It is necessary to determine the efficacy of SE in severe watery diarrheal disease of adults so that a decision can be formulated as to the adequacy and limitations of this solution in oral hydration.

B. SPECIFIC AIMS

To compare the effectiveness of a SE with GE in the hydration of patients with severe diarrheal disease due to cholera and E. coli as well as diarrhea of unknown etiology.

C. METHODS OF PROCEDURE

Patient population. A sample of male patients 16 to 50 years of age, being admitted to the Cholera Hospital because of uncomplicated acute watery diarrhea (less than two days) who have not received previous antibiotic during the last two weeks and who have given informed consent will be studied. When the apparent cholera season begins, during the fall of 1977 (approximately September), we will accept the first four male patients admitted to the hospital each day who meet the above criteria. Patients will continue to be admitted to the study until 150 patients have been included in the study.

Clinical Information. All patients will receive a standardized physical examination including an admission weight. Physical examination will note specifically signs of dehydration. Blood will be drawn for a CBC electrolytes, blood sugar, creatinine, specific gravity, and an acute sera for

antibody determination. A stool specimen will be obtained for culture, for microscopic examination, for sodium and potassium determination, for sugar determination, and two aliquots of stool will be frozen (to be examined for rotavirus antigen and heat-labile enterotoxin). Urine will be obtained for routine urinalysis, for sodium, potassium, osmolarity and specific gravity.

Treatment of Patients. Each patient will be stratified as to the clinical degree of dehydration (moterate or severe) and randomized in a double blind manner to one of two treatment groups.

Group I (Glucose-Electrolyte Solution) will be treated as follows. The initial replacement therapy for patients who are severely dehydrated will be by intravenous fluid using standard I.V. solutions (70 ml/ Kg over 1 hour). The I.V. will then be removed. Oral fluid will begin when tolerated to complete the rehydration (30 ml/Kg over 4 hours). Initial hydration for moderately dehydrated patients will be with oral fluid alone (70 ml/Kg over 4-6 hour period).

Maintenance Therapy of Group I will be by ad lib oral hydration using GE to replace stool losses. A goal for hydration will be to replace oral solution on an approximately one to one and a half basis, volume for volume. Stool passed during the initial rehydration period will also be replaced during this time.

Group II (Sucrose-Electrolyte Solution) will be treated exactly as Group I except that sucrose will be substituted for glucose in this solution.

Fluids to be used will be as follows:

Glucose Electrolyte Solution	Sucrose Electrolyte Solution
Na^+ 90 meq/liter	Na^+ 90 meq/liter
K^+ 20 meq/liter	K^+ 20 meq/liter
Cl^- 80 meq/liter	Cl^- 80 meq/liter
HCO_3 30 meq/liter	HCO_3 30 meq/liter
Glucose 111 mM/liter	**Sucrose 111 mM/liter**
which is made by:	which is made by:
NaCl 3.5q/liter	NaCl 3.5q/liter
$NaHCO_3$ 2.5q/liter	$NaHCO_3$ 2.5q/liter
KCl 1.5q/liter	KCl 1.5q/liter
Glucose 20 q/liter	Sucrose 40 q/liter

Follow up evaluations will be made as shown on the enclosed chart.

Maintenance replacement therapy will continue until the diarrhea stops. This is defined as a 24-hour period during which no watery stool has been passed. There will be no food restriction except for milk.

Tetracycline 500 mg QID (250 mg QID to those less than 30 Kg) for 2 days will be given to all patients. Intake and output records will be

maintained on a four hourly basis during the first 8 hours, then every eight hours using cholera cots. If patients are vomiting, oral fluids will be given by small amounts frequently: however, nasogastric tubes will not be used for vomiting. They may be used however, to allow patients to sleep if necessary. Patients will be discharged roughly 24 hours after diarrhea stops.

Failure of the oral solution will be either a failure to rehydrate or maintain hydration, or failure to maintain electrolyte balance. Failure of hydration will be based on objective criteria which will require the use of I.V. therapy (for moderate dehydration). Decision to use (or resume) I.V. therapy will be based on the following:

1) Failure of initial hydration; that is, failure of the patient to take oral fluid in quantitiy to match the estamated initial dehydration within six hours of admission, and associated with other clinical and laboratory signs (e.g. fall in body weight, poor skin turgor, rising pulse rate, increasing plasma specific gravity).
2) Failure to maintain hydration as shown by an increase in pulse rate, decrease in pulse volume, loss of body weight and an increase in plasma specific gravity of more than 1.030.
3) Deterioration of the general condition of the patient from the time of admission.

Patients who are restarted on I.V. fluids will again be tried on the oral-electrolyte solution which they previously received.

If electrolyte imbalance develops during therapy (Na > 125, > 155; K < 2.5, > 6.0) patients will be discontinued from the study and considered a treatment failure.

Patients will be asked to return 10 to 14 days after discharge for repeat serum specimen.

Special Lab. Studies:

Microbiology - E. coli from the admission stool culture will be tested for heat labile enterotoxin using the adrenal cell assay (or Elisa assay), and for heat stable toxin using the infant mouse assay. Antibodies to heat labile toxin will be determined by the microtiter adrenal neutralization assay.

Biochemistry - Stool sugars will be determined by measuring reducing substances in the stool, before and after hydrolysis, using clinitest tablets.

After the study is completed it should be possible to compare the sucrose with the glucose groups (using T Test and Chi Square Analysis) as follows:

1) Admission values: objective evidence of the severity of the disease should be same in both groups. Pathogens isolated from both groups should be the same.
2) Failure of oral fluids: defined as necessitating return to

intravenous fluids or dropping patient from study because of electrolyte abnormality.

3) Duration of diarrhea.

4) The volume of diarrheal stool.

5) The amount of fluids given, both intravenous and oral.

6) Any adverse reactions during therapy.

7) Ease of fluid administration, including acceptance of oral fluid by patients.

Randomization to either GE or SE will be done in a double blind manner. Mr. Akbar Ali, Biochemistry Branch Chief, will prepare the four solutions, marked A, B, C, D. Two will be glucose and two sucrose. Prospective stratification of patients will be by degree of dehydration; however, stratification by etiologic agent will be by retrospective analysis. The data will be transferred to IBM cards for data storage and analysis.

D. SIGNIFICANCE

From the results of this study, it should be possible to determine the efficacy of the sucrose-electrolyte solution in the treatment of watery diarrhea in adults. This is important in the treatment of watery diarrheal syndromes throughout the world, especially in rural or under-developed countries where medical facilities are limited.

E. FACILITIES REQUIRED

1) Office for investigators in study ward is already provided.

2) Laboratory spece: the routine bacteriology, biochemistry and immunology laboratories will be utilized.

3) Hospital Resources: the study ward will be used. Maximum of 12 hospital beds will be used per day.

It should be noted that these patients would be hospitalized regardless of the study, and no "extra" patient days are planned.

4) Animal Resources: E. coli from approximately 100 specimens will be tested for heat stable toxin which will require approximatley 1800 infant mice.

5) Logistical Support: We will need assistance from the epidemiology Branch to help secure the convalescent specimen. Also four hours of computer time is anticipated.

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Palmer, D.L., et al. Comparison of sucrose and glucose in oral electrolyte therapy of cholera and other severe diarrheas. In preparation

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SECTION III

1. Personnel Services

Name	Position	% of Effort	Annual Salary	Taka	Dollars
Dr S. Islam	Principal Investigator	20%	Tk. 36,384	7,277	
Dr D. Sack	Co-investigator	20%	$ 34,750		6,950
Dr Asma	"	20%	Tk. 27,084	5,417	
Epidemiology Tech.		10%	Tk. 20,484	2,048	
8 Study Nurses		10%	Tk. 16,284	13,027	
Akbar Ali	Study Technologist	10%	Tk. 32,076	3,208	
Dr Mahmud	Veterinarian	5%	Tk. 32,880	1,644	
Biochem Technician		10%	Tk. 27,084	2,708	
Animal House Tech.		20%	Tk. 20,000	4,000	
				39,329	6,950

2. Supplies

	Unit Cost	Amount required		
Office Supplies, misc.			1,000	
IBM Cards	$8/10,000	10,000		8
Computer Tapes	$8.19	2		16
Plastics, glassware				2,000
Infant mice	Tk. 3/-	1,800	5,400	
Tb syringes	$0.26	600		156
Needles, 27g.	$0.05	600		30
BHI media	Tk.0.16	1,800	288	
1½ ml vials, polypropylene		600		50
Nutrient agar, 1lb	$10.00	1		10
Clinitest tablets	$10.00/bottle	20		200
Computer time	Tk.650/hour	4 hours	2,600	
			9,288	2,470

			Taka	Dollars
3.	Equipment		0	
4.	Hospitalization		81,000	
	Routine tests		10,000	
			91,000	
5.	Outpatient follow up		7,500	
6.	CRL Transport 700 miles		500	
7.	Travel and Transportation of persons		0	
8.	Transport of things			800
9.	Rent, Communications and Utilities		0	
10.	Printing			
	Printing forms	Stencil 1,000 pages	200	
		Publication		300
		Xerox	500	
		Sub Total:	700	300
11.	Contractual Services	Tk.20/- x 100 (patient follow up)	2,000	
12.	Construction.		0	

B. BUDGET SUMMARY

Category	Year 1		Year 2		Year 3	
	Taka	Dollars	Taka	Dollars	Taka	Dollars
1. Personnel	39,329	6,950	None		None	
2. Supplies	9,288	2,470				
3. Equipment	-	-				
4. Hospitalization	91,000	-				
5. Outpatients	7,500	-				
6. CRL Transport	500	-				
7. Travel Persons	-	-				
8. Transportation of things	-	800				
9. Rent/Communication	-	-				
10. Printing and Reproduction	700	300				
11. Contractual service	2,000	-				
12. Construction	-	-				
Total:	140,317	10,520				

Total $ 19,874

Conversion Rate $1.00 = Tk.15/-

Consent Form - Sucrose vs Glucose Electrolyte Oral Solution
in the treatment of Diarrhea of Adults

The Cholera Research Hospital is carrying out studies to determine the most effective way to treat diarrhea. We would like you to participate in a study which is attempting to determine the effectiveness of two different sugar-salt solutions, given by mouth, in the treatment of diarrhea. If you decide to be admitted into the study you can expect the following:

1. You will be treated for diarrhea.

2. You would need to remain in the hospital until you have stopped having diarrhea for one day.

3. You will receive as part of your treatment one of two oral sugar-salt solutions. The solution will be marked "A", "B", "C" or "D".

4. While you have diarrhea, you will need to have blood tests each day. These are all routine tests and no special or hazardous tests will be done.

5. While diarrhea can be dangerous, there is no extra risk from participation in this study. If the oral solution is not adequate treatment, we may have to give intravenous solution.

6. You do not have to be in the study. If you decide against being in the study, you will be treated at CRL for your diarrhea.

7. You may ask questions about the study at any time.

8. You may withdraw from the study at any time, without jeopardizing your medical care.

9. Your medical records will be kept confidential.

10. We would like you to return for a blood test 10 days after being discharged.

If you agree to participate in this study, please sign your name here.

_____

Date _____

_____ Investigator's signature

Review Board on the Use of Human Volunteers

ABSTRACT SUMMARY

Sucrose vs Glucose Electrolyte Oral Solution
in the Treatment of Diarrhea in Adults

1. Approximately 150 adults, aged 16-50 years with uncomplicated watery diarrhea will be admitted into the study.

2. Risks of this study are very small. While dehydration and electrolyte imbalance are possible complications resulting from diarrhea, patients will be closely followed, 24 hours per day, by physicians to avoid these complications. Venapuncture blood samples will be required daily: this is a discomfort but not a significant risk.

3. Physicians will be present 24 hours daily during the study to detect any treatment failures at an early stage and take necessary action.

4. Patients will be identified by number. All records will be kept in a locked office. At the end of the study, identifying information will be removed from study data sheets.

5. Signed informed consent will be obtained from the patient. The study will be explained to the patients in Bengali and consenting patients will sign (or thumb print) the form. They will also have a copy of the Consent Form given to them.

6. N.A.

7. The patient will benefit by the treatment of his diarrhea. Society, especially of rural or under-developed countries, will benefit by

determining the efficacy of the oral solutions in the treatment of diarrhea.

8. Data will be collected from the patients hospital record. Blood, stool and urine will be collected from patients for study.

Sucrose vs Glucose Study

Patient Name _____

Hosp. Number _____

Study Number _____ A
1 2 3 4

Date of Admission day mo. yr
6 7 8 9 10 11

Time of Admission _____:_____
13 14 15 16

Age _____ months
18 19

Duration of diarrhea _____ hours
21 22

Description of stool ____ (1 watery, 2 liquid, 3 soft, 4 formed, 5 dysentery)
24

Vomiting ____ (1 yes, 2 no)
26

Oral Solution ____ (A 1, B 2, C 3, D 4)
28

Initial Clinical Assessment (to be completed on admission)

Dehydration ____ (1 severe (10), 2 mod-sev (7.5), 3 mild (5), 4 not apparent)
30

Rehydration fluid requirements _____ I.V. (ml.)
32 33 34 35

_____ P.O. (ml.)
37 38 39 40

Admission Weight _____ . ____ Kg.
42 43 45

Discharge Assessment

Stool Output during first 24 hours _____ ml/ Kg
47 48 49 50

Total Diarrheal stool _____ ml/ Kg
52 53 54 55

Total I.V. fluid given _____ ml / Kg
57 58 59 60

Oral solution used _____ ml/ Kg
62 63 64 65

Overall assessment ____ (1 succeeded, 2 failed)
67

Patient No. [ ][ ][ ]

Hours From Adm.	Day	STUDY SCHEDULE	EYES	PAIN	MUSCULO-SKELETAL	BODY WT (KG)	PULSE	BP	K	STOOL PER PERIOD	CUMM STOOL	STOOL DESCRIPTION	URINE	VOMIT	I.V. INTAKE	P.O. ORAL FLUID	P.O. (GAL. REC)
0	3																
4	C	CBC Sp. Gr.	Stool guiac														
8	D	Electrol osmol Sp. Gr. Glucose	Stool guiac														
16	E	NONE															
24	F	Electrol osmol Sp. Gr. Glucose	Stool guiac Rm 107														
32	G	NONE															
40	H	NONE															
48	I	Electrol osmol Sp. Gr. Glucose	Stool guiac Rm 107														
56	J	NONE															
64	K	NONE															
72	L	Electrol osmol Sp. Gr. Glucose	Stool guiac Rm 107														
80	M	NONE															
88	N	NONE															
96	O	Electrol osmol Sp. Gr. Glucose	Stool guiac Rm 107														

24

Patient Name _____
Patient Hosp # _____

BLOOD Patient Study # [ ][ ][ ]

URINE

STOOL

Date	Time	Hrs from Admit	Sp. gr 1.0__	Na	K	Cl	CO_2	Glucose	Osmol	Na	K	Osmol	Sp. gr 1.0__	Glucose 2hr pp Hgt
			31 34	35 40 41	93 95	96 97 98	29 30	22 26	52 57 60	62 63 64	66 67 68	70 71 72	74 75	77 78
		0 B												
		4 C												
		8 D												
		F												
		24 F												
		48 F												
		72 L												

Patient Name _____

Patient's Hosp Number _____

STUDY NUMBER [ ][ ][ ] (1 2 3) [Z] (4)

BLOOD: HCT [ ][ ] (6 7)

WBC [ ][ ][ ][ ][ ] (9 10 11 12 13)

Creatinine [ ][.] (15 17)

URINE [ ] (11) (1-normal, 2-abnormal)

STOOL:

MICROSCOPIC EXAM

[ ][ ] (21 22) rbc/hpf

[ ][ ] (24 25) fecal leukocytes/hpf

[ ] (26) Giardia (1-yes, 0-no)

[ ] (28) Ameba (1-cysts, 2-trophs, 3-trophs+rbc, 0-neg)

[ ] (29) Trichomonas (1-yes 0-no)

[ ] (30) Trichuris " "

[ ] (31) Hookworm " "

[ ] (32) Ascaris " "

[ ] (33) F. buski " "

[ ] (34) other _____

STOOL CHEMISTRY

Na [ ][ ][ ] (35-37)

K [ ][ ][ ] (39-41)

Cl [ ][ ][ ] (43-45)

CO_2 [ ][ ][ ] (48-50)

Osmol [ ][ ][ ] (52-54)

Darkield [ ] (55) (1-pos, 0-neg)

Culture [ ] (57) Vibrio (1-pos, 0-neg)

[ ] (58) NCV "

[ ] (59) Shig (0-neg, 1-S. dysT 2-S. dysII, 3-S. flex 4. S. boydii, 5. S. sonnei

[ ] (60) E. coli (0-neg, 1-LT, 2-ST, 3 LT-ST)

[ ] (61) other bact. pathogen _____

[ ] (62) Salmonella

STOOL ANTIGEN [ ] (64) Rotavirus

[ ] (65) LT