Attachment 1. 68

Date 24/4/83

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. M.R. Islam

Trainee Investigator (if any) _____

Application No. 83-014(P)

Supporting Agency (if Non-ICDDR,B) _____

Title of Study "EFFICACY OF SODIUM CITRATE TO REPLACE SODIUM BICARBONATE ORAL REHYDRATION SOLUTION" (LIMITED STUDY)

Project status:
( ) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form

Circle the appropriate answer to each of the following (If Not Applicable write NA).

Source of Population:
(a) Ill subjects — (Yes) No
(b) Non-ill subjects — Yes (No)
(c) Minors or persons under guardianship — Yes No

Does the study involve:
(a) Physical risks to the subjects — (Yes) No
(b) Social Risks — Yes (No)
(c) Psychological risks to subjects — Yes (No)
(d) Discomfort to subjects — (Yes) No
(e) Invasion of privacy — Yes (No)
(f) Disclosure of information damaging to subject or others — Yes (No)

Does the study involve:
(a) Use of records, (hospital, medical, death, birth or other) — Yes (No)
(b) Use of fetal tissue or abortus — Yes (No)
(c) Use of organs or body fluids — (Yes) No

Are subjects clearly informed about:
(a) Nature and purposes of study — (Yes) No
(b) Procedures to be followed including alternatives used — (Yes) No
(c) Physical risks — (Yes) No
(d) Sensitive questions — Yes (No)
(e) Benefits to be derived — (Yes) No
(f) Right to refuse to participate or to withdraw from study — (Yes) No
(g) Confidential handling of data — (Yes) No
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No

5. Will signed consent form be required:
(a) From subjects — (Yes) No
(b) From parent or guardian (if subjects are minors) — (Yes) No
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:

___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies)
✓ Protocol (Required)
✓ Abstract Summary (Required)
✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
✓ Informed consent form for subjects
✓ Informed consent form for parent or guardian
✓ Procedure for maintaining confidentiality
___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Ctree. for review.

Agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

M. Islam

Principal Investigator

Trainee

83-014(P)
25/4/83

SECTION 1 - RESEARCH PLAN

1. TITLE: EFFICACY OF SODIUM CITRATE TO REPLACE SODIUM BICARBONATE IN ORAL REHYDRATION SOLUTION.

2. PRINCIPAL INVESTIGATOR: Dr. Md. Rafiqul Islam

CO-INVESTIGATORS: Dr. Syed Masud Ahmed

Dr. Thomas C. Butler

3. STARTING DATE: June 1, 1983

4. COMPLETION DATE: December 31, 1983

5. TOTAL INCREMENTAL COST: US $ 2995.00

6. SCIENTIFIC PROGRAM: This protocol has been approved by the PATHOGENESIS & THERAPY WORKING GROUP.

Thomas Butler
PROGRAM HEAD

Date: 20-4-83

7. ABSTRACT SUMMARY:

A clinical trial is proposed to define the efficacy of sodium citrate as a substitute of sodium bicarbonate in the oral rehydration solution for the treatment of children below 2 years age suffering from diarrhoeal disease and also for those with cholera of any age. This study is planned to comprise 50 patients below 2 years suffering from acute watery diarrhoea and 50 patients of any age suffering from cholera. Study will be conducted in a double blind random way. Patients will be treated with oral solutions alone. The results will be compared to determine whether sodium citrate can correct acidosis resulting from continued base loss due to acute cholera and non cholera diarrhoeas.

8. REVIEWS:

(a) Research involving human subjects: _____

(b) Research Review Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

1. Objective:

The objective of this study is to compare the efficacy of sodium citrate with sodium bicarbonate in oral rehydration solution for correction of acidosis resulting for acute watery diarrhoea including cholera.

2. Background:

In acute watery diarrhoea, there are losses of watery as well as electrolytes like Na, K, Cl and bicarbonate in the stool. Proper replacement of water and electrolytes is the principal rationale behind the formulation of various intravenous and oral rehydration solution used in the management of acute diarrhoeal disease.

In our previous study "use of base-precursors as a substitute of bicarbonate in the oral rehydration solution" we have studied mostly non cholera patients above 2 years age with oral solutions containing either sodium citrate or sodium acetate in place of sodium bicarbonate and observed that either sodium citrate or sodium acetate is equally effective as of Na bicarbonate for the correction of acidosis secondary to diarrhoea (manuscript submitted for publication). The present study is an extension of the previous protocol to include children under two years suffering from any type of diarrhoea and patients of all age suffering from cholera. This study will complete the whole spectrum of age and diarrhoeal agents.

The present WHO recommended ORS packet contains bicarbonate which has short shelf life as the ingredients form lump in humid condition. This is the most single important disadvantage of the present WHO/ UNICEF packets. If ORS with sodium citrate instead of sodium bicarbonate is found to be equally effective in the treatment of infantile diarrhoea and cholera, thus this disadvantage will be removed and can be recommended for general use in the ORS for all types of diarrhoea and in all age group.

3. Rationale:

Sodium citrate is a palatable stable salt. There is less chance of the patient to become alkalotic since sodium citrate has to be converted to bicarbonate in the liver. Besides better shelf life, ORS packets containing sodium citrate presume to be more palatable and thereby acceptable to patients of all ages including infants.

B. SPECIFIC AIMS:

To evaluate the efficacy of sodium citrate in place of sodium bicarbonate in ORS for the correction of adidosis:

(i) in children under 2 years suffering from diarrhoea of any etiology and

(ii) in patients of any age suffering from cholera.

C. METHODS AND PROCEDURE:

1. Subjects:

50 patients below 2 years age with history of acute watery diarrhoea of less than 48 hours duration and clinically considered moderately dehydrated and another 50 patients of any age suffering from cholera will be selected for the study. Patients will be excluded from the study if they have received any antibiotics within a week prior to hospitalization. Severely malnourished children or patients with associated complications will be excluded from the study.

2. Randomization of patients:

Patients will be randomized to one of the two groups by choosing a slip of paper from an envelop.

3. Clinical procedures:

Selected patients will be admitted directly in the study ward. After randomization as described above, the following procedures will be followed until diarrhoea stopped.

(a) Body weight on admission and subsequently every 8 hours.

(b) Clinical history and thorough physical examination on admission.

(c) Vital signs (P/T/R) on admission and every 4 hours.

(d) Hydration status and clinical assessment will carefully be done every 4 hours.

(e) 2 ml venous blood will be drawn for Hct, electrolytes and specific gravity on admission, after 24 hours, and 48 hours, if diarrhoea continues, then after 72 hours also.

(f) Blood urea will be done from the serum blood on admission and after 24 hours.

(g) Stool will be sent for Dark field examination for V. cholerae and cultures in all plates for entero pathogens including E. coli, Shigella and Salmonella etc. Stool will be saved for detection of Rotavirus antigen by ELISA technique.

No intravenous fluid will be used for initial rehydration. Only one of the two oral solutions will be used. 75 ml/kg body weight will be given for initial rehydration and hydration status will be maintained by allowing ad libitum oral solution intake according to purging of the patient.

If a patient is unable to retain oral fluid due to persistant vomiting and becomes dehydrated then intravenous fluid 75 ml/kg B.W. will be used. After the calculated amount of fluid, I.V. will be discontinued and subsequent maintenance of hydration will be continued with one of the oral solution under trial. Adult patients suffering from cholera will receive tetracycline (500 mgm 6 hourly) for 2 days and children will receive Furazolidine for 5 days. Breast milk when available or diluted formula milk (1 : 1 ratio) will be allowed to children below 2 years and milk and bread will be given to older children and adults. Failure of the oral therapy will be defined as the inability to rehydrate, maintain hydration or failure to correct electrolyte imbalance.

4. Analysis of data:

After the study is completed, it should be possible to evaluate statistically the success of these two oral rehydration solutions after analysing.

(i) Failure of oral therapy as defined.

(ii) Duration of diarrhoea

(iii) Volume of diarrhoea stool

(iv) Amount of oral fluid

(v) Any complications during therapy

(vi) Acceptance of oral fluid by the patients.

D. SIGNIFICANCE:

From the result of this study, it should be possible to determine the comparative efficacy of these two types of ORS in the treatment of watery diarrhoea of any etiology under 2 years age and also in the treatment of cholera for any age. If ORS containing sodium citrate, is found to be equally effective as ORS containing sodium bicarbonate, it will increase shelf life of ORS packets which is or enormous importance from the storage point of view, especially in rural areas of developing countries.

E. FACILITIES REQUIRED:

Existing facilities will be adequate to complete the study.

F. COLLABORATIVE ARRANGEMENT: Nil

COMPOSITION OF ORAL FLUIDS TO BE USED
Gms/L

	Nacl	Kcl	$NaHco_3$	Na-citrate	Glucose
WHO ORS	3.5	1.5	2.5	-	20
ORS with Citrate	3.5	1.5	-	2.9	20

(Each type of fluid will provide Na - 90, K - 20, Cl - 80, Glucose - III and base 30 m.mols/L)

REFERENCES

1. R.A. Phillips: Water and Electrolytes losses in cholera. Fed Proc 23 : 705, 1964.

2. Hirschhorn N, et al: Decrease in net stool output in cholera during intestinal perfusion with glucose containing solutions. New Eng J. Med 279 : 176, 1968.

3. Nalin D.R., Cash R.A. et al: Oral Maintenance therapy for cholera in adults. Lancet 2 : 370, 1968.

4. Naik, N.V. et al: Oral rehydration in acute gastroenteritis in young children. Ind. Pediatrics 13 : 127 - 133, 1976.

5. Oral hydration in Rotavirus diarrhoea. A double blind comparison of sucrose with glucose - electrolyte solution. Lancet 5, Aug 5, 1978.

6. Islam MR et al: Efficacy of the base precursors acetate and citrate in oral rehydration solution for the correction of acidosis secondary to diarrhoea (Manuscript submitted for publication).

SECTION - III

DETAILED BUDGET:

1. Personnel services:

Name	Position	% of effort	Project Requirements Taka	Dollar
Dr. M. R. Islam	Principal Investigator	25%	15000	-
Dr. Masud Ahmed	Cl. Research Fellow (Co-Investigator)	50%	9000	-
Mr. Akbar Ali	Head, Biochemistry (Co-Investigator)	10%	4000	-
Dr. T. Butler	Consultant	-	-	-
Microbiology Technician	1 person/	1 person/month	4000	-
Cl. Path. Technician		1 person/ month	4000	-
Biochemistry Technician		1 person/ month	4000	
Veterinarian			3000	
			43000	-

2. Supplies and Materials:

	Taka	Dollar
Stool culture - X 100 specimens	2500	-
Stool D/F X 100 specimens	500	-
Hct & Sp. Gravity - X 300 specimens	500	-
Electrolytes - X 300 specimens	400	-
Adrenal cell assay - X 200 specimens	3600	-
Infant mouse assay - X 100	1000	-
ELISA test - 100 specimens X 100	300	-
Glass ware, plastic syringe, needle etc	-	200
500 ORS packets (100 X 5) - Taka 2 per packet	1000	-

		Taka	Dollar
3.	Equipments - Nil		
4.	Hospitalization - 100 X 3 days X Tk. 150/day	45000	-
5.	Outpatient - Nil		
6.	Transport - Nil		
7.	Travel - Nil		
8.	Transport of things - Nil		
9.	Rent - Nil		
10.	Printing	1000	
11.	Contractual services - Nil		
12.	Construction - Nil		
	TOTAL	Tk. 55900	US $ 200

Incremental cost excluding personnel salary

Total Incremental cost US $ 2795

Conversion rate @ US $ = Tk. 20

GRAND TOTAL US $ 2995

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. 50 patients below 2 years age with history of acute watery diarrhoea of less than 48 hours duration and another 50 patients of any age suffering from cholera will be selected for the study. Patients suffering from other complications including severe malnutrition will be excluded from the study. Half of these patients will receive standard ORS containing sodium bicarbonate and another half will receive an oral solution containing sodium citrate in place of sodium bicarbonate. Efficacy of these two solutions will be compared after the double blind study is over.

2. There is no potential risk involved in this study.

3. Patients will be under constant observation and appropriate treatment will be provided whenever any complications arises.

4. Only patients identification number will be used during analysis of results.

5. Signed consent will be obtained from the patients or legar guardians.

6. No special interview except simple clinical history will be necessary.

7. Patients will be benifitted from this study. It ia anticipated that the shelf life of citrate containing ORS will be more than the bicarbonate containing ORS packets.

8. Hospital records and body fluid examination will be necessary.

CONSENT FORM

STATEMENT READ AND EXPLAINED VERY CLEARLY TO THE SUBJECT WHEN CONSENT IS OBTAINED

"EFFICACY OF SODIUM CITRATE TO REPLACE SODIUM BICARBONATE IN ORAL REHYDRATION SOLUTION"

The ICDDR,B is carrying out research to develop most economic but effective way to treat diarrhoea in a very simple way like oral rehydration therapy. We will be trying 2 kinds of oral solutions to treat your diarrhoea. They were found reasonably effective in previous studies without any serious complications. We want to compare the relative effectiveness of these 2 types of oral rehydration solutions to know the best type for the treatment of acute watery diarrhoea. We like you to participate in the study for the well being of mankind. If you decide to participate in our study, you can expect that:

1. You will be given best possible care for your diarrhoea.
2. You will be needed to stay at least 3 days for even more until your diarrhoea stops.
3. While you are in hospital, we want to test a total of 4 samples of blood (about 2-3 c.c. each time) to know your health position. These are all routine tests.
4. If the oral solution given to you fails to treat you by any chance or cause any sort of unbearable discomfort, you will be taken off the study and will be treated with proper intravenous fluid.
5. If you do not like to participate in the study, still you will be treated like other in this hospital.
6. Bedises, if you wish, you are at liberty to withdraw from the study at any time without any obligations and jeopardizing your medical care and treatment.

Understanding and realizing fully if you are willing voluntarily to participate in the study, then please sign your name or give Left thumb impression below.

Signature of Investigator

Date: _____

Signature: _____
or Left thumb impression of the patient's or legal guardian in case of child.

ICDDR,B Admission No.: _____

আন্তর্জাতিক উদরাময় রোগ গবেষণা কেন্দ্র
ঢাকা, বাংলাদেশ

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র ডায়রিয়া রোগের সস্তা কিন্তু কার্যকরী চিকিৎসা উদ্ভাবনের চেষ্টা চালিয়ে যাচ্ছে। এর মধ্যে মুখে খাওয়ার স্যালাইন অন্যতম। আমরা আপনার শিশুর ডায়রিয়া চিকিৎসার জন্য দুই ধরণের খাওয়ার স্যালাইন দিয়ে চিকিৎসা করব। পূর্বের গবেষণায় এই স্যালাইনের কার্যকারিতা পরীক্ষিত হয়েছে। আমরা এই দুই ধরণের খাওয়ার স্যালাইনের তুলনামূলক কার্যকারিতা পরীক্ষা করে ডায়রিয়া চিকিৎসার জন্য কোনটি সর্বোত্তম জানতে চাই। আমরা চাই সমাজের বৃহৎ মংগলার্থে আপনার শিশু এই গবেষণায় অংশগ্রহণ করুক।

আপনি যদি গবেষণায় অংশগ্রহণ করতে ইচ্ছুক হন, তা'হলে নিম্নলিখিত ব্যবস্থাদি গ্রহণ করা হবে -

১। আপনাকে সর্বাধিক উন্নত চিকিৎসা দেয়া হ'বে।

২। আপনাকে কমপক্ষে তিনদিন কিংবা পায়খানা ভাল না হওয়া পর্যন্ত হাসপাতালে থাকতে হ'বে।

৩। হাসপাতালে থাকাকালীন সময়ে আমরা আপনার শিশুর কাছ থেকে মোট চারবার সামান্য পরিমাণে (প্রতিবার ২ সি সি থেকে ৩ সি সি) রক্ত পরীক্ষার জন্য নেব। রোগীর অবস্থা জানার জন্য এর প্রয়োজন হবে।

৪। যদি খাওয়ার স্যালাইন দিয়ে চিকিৎসা কোন কারণে সফল না হয়, আপনার শিশুকে তা'হলে গবেষণা থেকে প্রত্যাহার করে নেয়া হ'বে এবং শিরার স্যালাইন দিয়ে চিকিৎসা করা হবে।

৫। আপনি যদি গবেষণায় অংশগ্রহণে রাজী না থাকেন তবুও অন্যান্য রোগীর মত আপনার শিশুর চিকিৎসা করা হ'বে।

৬। এছাড়াও গবেষণা চলাকালীন যে কোন সময়ে ইচ্ছা করলে আপনি আপনার শিশুর নাম প্রত্যাহার করে নিতে পারবেন কোন প্রকার বাধ্যবাধকতা ছাড়াই। এরদ্বারা কোন ভাবেই আপনার রোগীর চিকিৎসা বিঘ্নিত হবে না।

সব কিছু ভালভাবে জেনে এবং বুঝে যদি আপনি স্বেচ্ছায় গবেষণায় অংশগ্রহণ করতে রাজী থাকেন, তা'হলে নীচে আপনার নাম স্বাক্ষর/কিংবা নাম হাতের বুড়া আংগুলের ছাপ দিন।

গবেষকের স্বাক্ষর ও তারিখ

রোগীর অভিভাবকের স্বাক্ষর/টিপসহি