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ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 27/12/83

Principal Investigator A.N. ALAM

Application No. 83-048(P)

Title of Study Trial of a wheat-based ORS in the treatment of acute diarrhoea

Trainee Investigator (if any) ____

Supporting Agency (if Non-ICDDR,B) ____

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).

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — (Yes) No
2. 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)
3. 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
4. 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 — NA 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 document's being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit (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
   X 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 Cttee. 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.

Principal Investigator

Trainee

## SECTION I - RESEARCH PROTOCOL

1. Title : Trial of a Wheat-based ORS in the treatment of acute diarrhoea

2. Principal Investigator : Dr. Ahmed Nurul Alam

   Co-Investigator : One physician (to be named)

   Dr. A.M. Molla

   Dr. M.M. Rahaman

   Consultant : Dr. W.B. Greenough III

3. Starting Date : January 1, 1984

4. Completion Date : June, 1984

5. Total Direct cost : US $ 2,404

6. Scientific Programme Head : M M Rahaman

   Date : 19/12/1983

7. Abstract Summary:

Wheat extract consisting of partly hydrolysed starch of the wheat grain and protein will be used to replace sucrose or glucose in a standard oral rehydration solution. Its acceptability and efficacy for rehydration of acute diarrhoeal children between 1-8 years of age will be evaluated in a case-control study.

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. Objectives: The aim of this limited study will be to evaluate the relative efficacy of a partly hydrolysed wheat-based electrolyte solution as compared to glucose-electrolyte solution for oral rehydration of children with acute diarrhoea.

2. Background: The efficacy of oral rehydration therapy in replacing the loss in the stool of water and salts in watery diarrhoea has been well established[1-4]. It has almost eliminated the need for I.V. fluid therapy except in most severe cases. Although oral therapy is no more effective than intravenous, it is inexpensive and comfortable for the patient. The discovery of glucose-facilitated transport of sodium and water in the small intestine[5] led to the use of glucose-salt solution for effective rehydration of patients with acute watery diarrhoea. However, glucose absorption is rate limiting and increasing its concentration leads to osmotic diarrhoea. Possible ways of further enhancing the absorption of sodium (and water) in acute diarrhoea had been tried. Recent studies by Molla et al[6] and subsequently by Patra et al[7] have shown that 30-50g of rice powder to be as effective or even superior

to glucose or sucrose in a standard electrolyte solution for the treatment of acute diarrhoea. The carbohydrate of rice is predominantly starch and it is speculated that rice starch is digested by intraluminal enzymes slowly releasing the glucose molecules which stimulate optimum sodium absorption without imposing an 'osmotic penalty'. In a subsequent study, Dr. Molla et al have observed a significant reduction of both stool volume (about 50%) with less intake of ORS following the use of 80g rice powder instead of sucrose or glucose (in the WHO recommended electrolyte solution) both in children and adults (unpublished observation).

Although rice is the principal staple grain for a large population of the world particularly of South East Asia, its consumption in the world is exceeded by that of wheat. In Bangladesh, rice is still the principal food. Due to recurrent natural calamities, wheat cultivation, which is more economic, has been expanding as a viable alternative cereal grain and today, it constitutes over 20 percent of the staple cereal food and its popularity is increasing.

Wheat extract, which is a partly hydrolysed starch of the wheat grain, has recently been prepared by enzymatic digestion of powdered wheat grain[8]. The extract is most suitable for spray-drying and is completely soluble in water resulting in a low-bulk solution. This preparation is rich in protein (lysine being limiting amino acid), low in fat (0.5%) and lactose content and it contains some vitamins and most of the minerals. Calculated on the basis of dry matter, it contains carbohydrate (87%), protein (11.5%), fat (1.5%) and ash (1.8%). Carbohydrates in the extract include:

| | | |
|---|---|---|
| Glucose | 3% | of total carbohydrate |
| Maltose | 60% | " " |
| Maltotriose | 19% | " " |
| Higher maltosaccharides | 15% | " " |
| Isomaltose, sucrose, fructose | 2% | " " |

Energy: 3.99 kcal/g dry wt.

In a preliminary study, we have tested its acceptability and digestibility[9] and its use as an alternative source of nitrogen and calorie repletion during rehabilitation of malnourished children[10]. The carbohydrate of the extract is the hydrolysis product of starch plus sugars originally present in the wheat. In vitro acid hydrolysis converts about 80% of the wheat extract into glucose so that if 50g is added to a liter of ORS, about 40g glucose will be liberated in the intestinal lumen. The

osmolarity of a 5% solution of the wheat-extract as measured after adding WHO-recommended electrolytes was found to be 280 which is almost isosmolar. On the otherhand, a solution of 5% dextrose with WHO recommended electrolyte will give an osmolar strength of 490, which may produce osmotic diarrhoea and induce vomiting. In a recent study[11], the wheat extract mixed with milk was found to be beneficial in the management of severe diarrhoea in malnourished children after initial rehydration. No untoward effects eg. osmotic diarrhoea, hypernatraemia etc. were observed following the intervention. Wheat extract, being partially digested product of wheat grain ( a cereal like rice), is expected to show similar or even better results in terms of reduction of stool volume, mean duration of diarrhoea and reduction in the quantity of ORS requirement.

## B. SPECIFIC AIM

To assess the relative efficacy of a wheat-based electrolyte solution as compared to glucose electrolyte solution as oral therapy in acute diarrhoea.

## C. METHODS OF PROCEDURE

Fifty children between 1-8 years admitted to the treatment centre of ICDDR,B., Dhaka hospital with normal nutritional status and watery diarrhoea of less than 72 hours duration with clinical signs of moderate to severe dehydration will be selected for the

present study. Routine clinical examination will be done on each patient on admission. Patients with signs of systemic disease, severe malnutrition or other complications like bronchopneumonia, otitis media etc. or who received antibiotics during the preceeding week will be excluded from the study. The nature of the study will be explained to the parents and written consent will be obtained from them prior to the study. Fifty children comparable at the time of hospital admission with regard to age, sex and duration of diarrhoea, will be randomized following the permuted block design so as to ensure equal number of subjects in both the treatment groups where electrolyte content of both solutions will be similar as recommended by the World Health Organization ($Na^+$ 90 mmol/L, $K^+$ 20 mmol/L, $Cl^-$ 80 mmol/L and $HCO_3^-$ 30 mmol/L). One group will receive an electrolyte solution containing 50g of wheat powder per litre and the other group will receive WHO-recommended glucose-electrolyte solution. <Table 1> The extract available as powder and the electrolytes will be packaged separately. The solution will be prepared by adding the electrolytes to the wheat powder dissolved in a litre of water. Normal hospital diet will be allowed soon after initial rehydration. Mother will be encouraged to continue breast feeding and plain water will be offered ad libitum. Patients with severe dehydration will be rehydrated by standard intravenous fluid within 1-2 hours following the WHO guidelines[12] and will be offered the study solution after initial

rehydration. Patients with initial mild and moderate dehydration will be treated by wheat-based ORS from the beginning. Body weight will be recorded on admission and every 8 hours. Any vomitus from study patients will be measured and recorded. No antibiotics will be given during the study period. Any patient requiring antibiotic will be taken out of the study. 2 ml blood will be drawn for the estimation of electrolytes, HCT and specific gravity on admission and repeated at 24 hours and before discharge. Eight-hourly intake output charts will be maintained. Plastic uribags will be used to collect urine separately. Microscopic examination and culture of stool samples will be carried out in each patient on admission.

The rate of purging, change in body wt., serum specific gravity, urine output, pre-and post-hydrolysis sugar content of stool will be measured every 24 hours to compare the two kinds of oral therapy. Patients will be discharged (on an average after 3 days) after passing the first formed stool.

Failure of treatment

Patients who require I.V. fluid after initiation of oral fluid or who develop signs of any complications during the therapy like severe vomiting, high fever, electrolyte abnormality, decreased body weight upto or below the admission weight etc. will be declared as failure and be treated accordingly. They will be

considered as a separate group while determing the outcome. Before declaration of failure, finger specimen for HCT, Sp. gravity will be taken.

D. FACILITY REQUIRED

Biochemical procedures will be carried out in ICDDR,B.

E. COLLABORATIVE ARRANGEMENTS: None

F. ANALYSIS OF DATA

Statistical analysis will be done using the students 't' test.

G. SIGNIFICANCE

Wheat-based ORS, if found to be as effective as the WHO recommended glucose-electrolyte solution, will pave the way of using a cereal other than rice for the treatment of diarrhoea, as the major proportion of global population depend on wheat as the principal cereal.

Glucose polymers are known to be powerful stimulants of sodium and water absorption in healthy subjects[13]. By converting starch into soluble carbohydrates, will enable us it will be possible to make an ORS solution which will not only be calorie-dense but also provide better nutritional support facilitating early rehabilitation of malnourished children with diarrhoea.

## SECTION III - BUDGET

1. Personnel Services

| Name | Position | % of efforts | Annual Salary Tk. | Dollar |
|---|---|---|---|---|
| Dr. A.N. Alam | Principal Investigator | 30% (6 month) | 27,000 | |
| Physician to be named | Co-investigator | 30% (6 month) | 10,800 | |
| Dr. A.M. Molla | " | - | | |
| Dr. M.M. Rahaman | " | - | | |
| Dr. W.B. Greenough | Consultant | - | | |
| | | | 37,800 | |

2. Supplies and Materials

A. Laboratory Test

| | | | |
|---|---|---|---|
| Blood test Hct % and sp. gravity | 12.0x150 | = | 1,800 |
| Blood for Electrolytes | 22.0x150 | = | 3,300 |
| Stool microscopy | 2.50x50 | = | 125 |
| Stool culture | 15x50 | = | 750 |
| ELISA for rotavirus | 10x50 | = | 500 |
| E. coli toxin assay (ST & LT) | 14.50x50 | = | 725 |
| Stool glucose contents | 40x6.50 | = | 12,000 |

3. Equipment - Nil

4. Patient hospitalization (3x50=150 Hospital day) 150x200 = 30,000

5. Outpatient care - Nil

6. ICDDR,B transport - Nil

7. Transport of material - Nil

(Wheat extract is kindly provided by Prof. Dahlquist)

8. Rent, communication - Nil

9. Printing, and reproduction - Nil

| | | Annual Salary Tk. | Dollar |
|---|---|---|---|
| 10. | Construction | - Nil | |
| 11. | Medicine | 2,000 | |
| | | 51,200 | |

Grand total Tk. 37,800 + 51,200 = 89,000

Overhead cost (10%) = 8,900

Tk. 97,900

Incremental cost = Tk. 97,900 - 37,800 = Tk. 60,100

= $ 2,404

Table 1

Compositions of the Types of ORS Tube Used in the Study

| Ingredients (gms/L) | Sol A | Sol B |
|---|---|---|
| NaCl | 3.5 | 3.5 |
| Kcl | 1.5 | 1.5 |
| $NaHco_3$ | 2.5 | 2.5 |
| Glucose | 20 | - |
| Wheat powder | - | 50 |
| Osmolality | 330 | 280 |

## List of references


1. Darrow DC, Pratt EL, Flett J, Gamble AH, Wiese F. Disturbances of water and electrolytes in infantile diarrhoea. Pediatrics 1949;3:129-56.

2. Chatterjee HN. Control of vomiting in cholera oral replacement of fluid. Lancet 1953;ii:1063.

3. Harrison HE. Symposium on clinical advances; treatment of diarrhoea in infancy. Pediatr Clin N Am 1954;1:335-48.

4. Meneghello J, Rosselot J, Aguilo C, Moncreberg F, Unduragga O, Ferrerio M. Infantile diarrhoea and dehydration: ambulatory treatment in a hydration centre. Adv Pediatr 1960;11:183-208.

5. Schultz SG, Zalusky R. Ion transport in isolated rabbit ileum. II. The interaction between active sodium and sugar transport. Z Gen Physiol 1964;47:1043-59.

6. Molla AM, Sarker SA, Hossain M, Molla A and Greenough III, WB. Rice-powder electrolyte solution as oral therapy in diarrhoea due to Vibrio cholerae and Escheria coli . Lancet, 1982;i:1317-19.

7. Patra FC, Mahalanabis D, Jalan KN, Sen A and Banerjee P. Is oral rice electrolyte solution superior to glucose electrolyte solution in infantile diarrhoea? Arch. Dis. Childhood, 1982;57:910-12.

8. Dahlquist A, Bjorck I, Theander O and Conrad E. New products from wheat. Food Chemistry, 1983;

9. ICDDR,B protocol No.82-011 (P). Acceptability and digestibility of wheat syrup. Alam AN et al

10. ICDDR,B protocol No.83-003(P). Wheat syrup as a caloric supplement for improving the rate of weight gain in children. Alam AN et al

11. Suthutvoravut U, Tontisirin K, Varavithya W, Valyasevi A, Bjorck I and Dahlquist A. Effect of a mixture of wheat extract and milk on diarrhoea in malnourished children. Program and abstracts on Fourth Asian Congress of Nutrition. November 1-4, 1983, Bangkok.

12. World Health Organization. A manual for the treatment of diarrhoea. Programme for control of Diarrhoeal Diseases, World Health Organization, Geneva (WHO/CDD/SER/80.2).

13. Sandhu BK, Jones BJM, Brook CGD and Silk DBA Oral rehydration in acute infantile diarrhoea with a glucose polymer electrolyte solution. Arch. Dis. childh-od. 1982;57:152-54.

## Abstract Summary

(1) Fifty children, between 1-8 years, admitted to the treatment centre of ICDDR,B with watery diarrhoea of less than 72 hours duration and moderate to severe dehydration will be taken for study.

(2) There is no potential risk involved in the study.

(3) Not applicable.

(4) All records will be kept strictly confidential with the Principal Investigator. If data is put on computer tapes, study patients will be referred to by number only.

(5) Informed consent (signed or thumb impression) from guardians will be obtained prior to the study. There is no procedure in this study which may unmask the privacy of the subject.

(6) Interview will be taken from the guardians only related to their medical history.

(7) Wheat has become popular among the Bangladeshi population as the second major staple food. A wheat based ORS, if found as effective as the WHO recommended ORS, can be used as an alternative oral rehydration therapy for the treatment of diarrhoea. The patients will gain by the treatment of their illness and the society will gain by exploring an alternative substrate for a cereal-based home remedy for diarrhoea.

(8) 2 cc of venous blood will be taken at 0 hour and 24 hours for the determination of Hct & Serum electrolyte.

# সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র খাবার স্যালাইনের ব্যবহারের জন্য বিভিন্ন প্রকার দেশীয় সিরিল জাতীয় খাদ্য পরীক্ষা করে দেখছে। গত কয়েক দশকে গম বাংলাদেশে একটি অন্যতম জনপ্রীয় প্রধান খাদ্যে পরিনত হয়েছে। আমরা খাবার স্যালাইনে গমের সুঁজি ব্যবহার করে বর্তমানের ব্যবহৃত খাবার স্যালাইনের সাথে ডাইরিয়া রোগে আক্রান্ত শিশুদের চিকিৎসার ক্ষেত্রে এর তুলনামূলক উপযোগীতা পরীক্ষা করে দেখতে চাই। আমরা চাই সমাজ ও মানবতার বৃহত্তর স্বার্থে আপনি এই গবেষনায় আপনার শিশুকে অংশগ্রহণ করতে অনুমতি দিবেন।

আপনি যদি স্বেচ্ছায় রাজী থাকেন, তাহ'লে আমরা নিম্নলিখিত ব্যবস্থাদি নেব:

১। আপনার শিশুকে কমপক্ষে ৪৮ ঘন্টার জন্য হাসপাতালে থাকতে হবে।

২। আপনার শিশুকে সম্ভাব্য সুচিকিৎসা দেওয়া হবে এবং বর্তমানে ব্যবহৃত খাওয়ার স্যালাইন কিংবা গমের সুঁজি সহযোগে তৈরী খাওয়ার স্যালাইন দ্বারা চিকিৎসা করা হবে।

৩। শিরা থেকে ২ সি সি রক্ত পরীক্ষার জন্য নেওয়া হবে। একবার ভর্তির সময় এবং পরে ২৪ ঘন্টা পর এই মোট দুইবার রক্ত পরীক্ষার জন্য নেওয়া হবে।

৪। কোন কারনে খাওয়ার স্যালাইন দিয়ে চিকিৎসা সম্ভব না হ'লে শিরায় স্যালাইন দিয়ে চিকিৎসা করা হবে।

আপনি যদি গবেষণায় অংশগ্রহণ করতে রাজী নাও হন, তবুও আপনার শিশুকে হাসপাতালের প্রথামত চিকিৎসা দেওয়া হবে।

গবেষনা চলাকালীন যে কোন সময়ে আপনি ইচ্ছা করলে আপনার শিশুকে প্রত্যাহার করে নিতে পারেন, এতে আপনার শিশুর চিকিৎসার কোন ত্রুটি হবে না।

আপনি যদি উপরোক্ত বিষয়গুলি সম্বন্ধে রাজী থাকেন তা'হলে নীচে আপনার স্বাক্ষর কিংবা বাম হাতের বৃদ্ধাংগুলের ছাপ দিন।

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গবেষকের স্বাক্ষর ও তারিখ

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অভিভাবকের স্বাক্ষর। টিপ সহি

# CONSENT FORM

ICDDR,B is carrying out researches to explore various locally available cereals as substrate for the cereal-based oral rehydration solutions. Wheat is becoming a popular staple food in Bangladesh during the last decade. We want to study the efficacy of a wheat-based ORS in comparison to standard ORS in rehydrating children with acute diarrhea. We will request you to permit your child to enter into the study for the benefit of society and mankind.

If you voluntarily agree to particpate, we will do the followings:

(1) Your child would have to stay for 48 hr (2 days) in hospital.

(2) Your child will be given best possible care in the hospital and treated with either wheat ORS or standard ORS solutions.

(3) 2 cc of venous blood will be taken on the day of admission and 24 hour later to determine serum electrolytes and specific gravity.

(4) If ORS fails for any reason, treatment will be instituted with intravenous saline Promptly.

Even if you do not want to participate in the study you will be provided with the usual treatment in the hospital. You can withdraw at any time, if you wish, which would not hamper in any way your child's treatment and care.

If you agree to the above facts, please give your consent by signing or giving your left thumb impression below.

Signature of Investigator with date

Signature/left thumb impression of patient's Guardian