Attachment 1. Date 17/10/90

(FACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr.R.N.Mazumder Trainee Investigator (if any) _____

Application No. 90-017 Supporting Agency (if Non-ICDDR,B) _____

Title of Study Controlled trial of an energy dense porridge of rice or rice plus lentil liquefied with added amylase rich germinated wheat flour in children aged 6months to 36 months with acute dysentery

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 (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 Cttee. for review.

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

Ramendra Nath Mazumder

Principal Investigator 17/10/90 Trainee

90-017
17/10

SECTION I - RESEARCH PROTOCOL

1. TITLE : CONTROLLED TRIAL OF AN ENERGY DENSE PORRIDGE OF RICE OR RICE PLUS LENTIL LIQUIFIED WITH ADDED AMYLASE RICH GERMINATED WHEAT CEREAL FLOUR IN CHILDREN AGED 6 MONTHS TO 36 MONTHS WITH ACUTE DYSENTERY (i.e.,BLOODY DIARRHOEA)

2. PRINCIPAL INVESTIGATOR : Dr. R.N.Mazumder

CO-INVESTIGATORS : Dr. A.Q.M.Iqbal Kabir

Dr. Mohammod Ali

CONSULTANT : Dr. F.C.Patra

PROJECT CORDINATOR : Dr. Dilip Mahalnabis

3. STARTING DATE : As soon as protocol is approved

4. COMPLETION DATE : Two years from the date of starting

5. TOTAL DIRECT COST : US$ 160,000

POSSIBLE SOURCE OF FUNDING : S D C

6. SCIENTIFIC PROGRAME : This protocol has been approved by the clinical Sciences Division

Signature of the Associate Director, CSD

Date 17/10/90

7. ABSTRACT SUMMARY

To evaluate the role of liquefied energy dense diet in increasing the calorie and nutrient intake in infants and young children aged 6 months to 36 months with acute bloody diarrhoea, patients will be randomized to receive either of the three diets in the ICDDR'B hospital : i) the experimental group will receive an energy dense porridge of rice or rice plus lentil, liquefied by adding amylase rich germinated wheat cerial flour (group 1), ii) one control group will receive a semi-solid porridge of rice or rice plus lentil of same energy density (group 2), iii) another control group will receive a porridge of rice or rice plus lentil, liquefied by adding water to the same viscosity as the diet of group 1 (group 3). A total of 192 patients, 64 in each group will be enrolled over a period of two years. Besides standared case management, four meals of the assigned porridge (200 ml/kg/24 hours) will be offered every day until discharge.

Patients will be selected from the triage area of Clinical Research center of ICDDR'B. Children fulfilling eligibility criteria and attending between 8 am and 12 noon on week days will be considered for inclusion into the study.

A detailed medical history and clinical information will be recorded on admission. Stool, urine, and 3 ml blood will be collected on admission and 2 ml on day 5 and day 10.

Pre-randomization history, physical examination, social and anthropometrical data will be recorded on a pretested data form. Randomisation will take place after a patient's gurdian has signed the consent form.

No deviation from routine case management of Clinical Reserch Center of ICDDR'B will take place except for the type of food offered and that the number of feeds will be standardised.

Outcome will be juciged by : (1) Quantity of daily food intake (calories and macro-nutrients) and during total duration of dysentery from the experimental porridge on a realistic number of feeds per day; (2) Quantity of daily breastmilk intake in breastfed children and during the total duration of illness (measured by weight difference before and after feeding using a precision balance); (3) Cumulative stool frequency by day 3 and day 5. Secondary response variable : (5) Acceptance of the experimental porridge by the children and by the mothers.

9. REVIEWS :

i. Ethical Review Commitee_____

ii. Research Review Commitee_____

iii. Director's Signature and remarks, if any -

_____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective :

i) In a randomised trial we will evaluate the role of liquefied energy dense porridge preparations in increasing the calorie and nutrient intake in infants and young children from 6 to 36 months with acute dysentery (particularly shigellosis).

2. Background :

Of the 15 million deaths occurring each year in children under five years in the developing world approximately 4 million are associated with diarrhoea. Based on ICDDR,B studies, and extrapolating them to world wide figures it has been estimated that approximately 0.7 to 0.8 million deaths occur each year in children under 5 years of age with dysentery. These estimates are based almost entirely on data obtained from Bangladesh. Comparable data are not available from other parts of the world. A case fatality rate of 1.2% has been reported for endemic shigellosis in the ICDDR'B Matlab, treatment center (Black et all 1980). At the ICDDR'B in Dhaka mortality rate in patients with shigellosis were 3.5% for those under 1 year of age and 0.3% for all other ages including adults (Stoll et al 1982). However mortality rates as high as 6% have been reported during epidemics of shigella dysenteriae type 1 (Rogerie et al 1986, Huppertz et al 1986). Other than mortality the primary negative effect on the health of diseased children who do not die from dysentery worsen

their nutritional status (Black et al 1984). Basic supportive therapy for Shigella dysentery includes use of ORS and early feeding which is similar for all diarrhoeal illness. Clinical dehydration, however, is not frequently seen with dysentery but when it occurs it indicates an increased severity of disease (Streulens, Bennish). Antibiotics are the cornerstone of treatment for shigellosis. Eradication of these large bowel invasive organisms shortens the clinical illness substantially. Shigella infections occur most frequently in children in developing countries in the age group 1 to 4 years (Stoll et al, 1982; Boyce et al). Under the age of one year, Shigella causes disease only about 1/2 to 1/3 frequently but, when it occurs, the disease is more likely to be severe (Duncan et al, 1981; Martin et al, 1983; Struelens et al, 1985). From a number of studies (Duncan et al, 1981; Martin et al, 1983; Struelens et al, 1985; Clemens et al, 1986), certain risk factors for death have been recognized which are malnutrition (<70% weight for age), absence of breastfeeding, age less than 1 year, moderate to severe dehydration, and lack of fever or hypothermia. Malnutrition being both a risk factor for mortality from shigellosis and an important adverse consequence of the disease, nutritional management of children with Shigella disease assumes importance. During the acute phase of the disease, anorexia is an important constraint to liberal feeding of children with shigellosis, particularly those who have severe clinical disease. A recent controlled trial in Peru (Brown et al, 1988 - Unpublished) showed that energy intake at a level of 100 kcal/kg/24 hours from the first day of treatment of children

with acute diarrhoea had a significantly better nutritional outcome on day 8 and day 14 of treatment compared to the group treated with restricted food intake during the first 48 hours of treatment. Shigellosis being predominantly a large bowel disease small bowel function is likely to be retained to a large extent; therefore dietary intervention in the acute phase of the disease may be very effective.

"Dietary bulk" (high volume/viscosity) remains a major problem in the nutritional management of young children (ULF Svanberg 1987). The high energy requirement of young children, together with their limited stomach capacity, make it impossible for them to eat enough food, particularly if the number of meals per day is low (Svanberg 1987, R.P.Kingakono 1987). A high dietary bulk is common in most developing countries, including Bangladesh, where weaning foods are based mainly on starchy staples, such as corn or rice (T. Gopaldas 1987). It is, therefore, vital that simple means to be established whereby the calorie density of traditional weaning foods may be enhanced while maintaining a thin consistency.

Two examples of such traditional, bulk-reducing methods have attracted the attention of researchers : the first is sprouting (malting or germination) of cereals (Brandtzaeg et al. 1981; Mosha and Svanberg 1983) and of legumes; the second is fermentation. In germinated cereal flours, advantage is taken of the amylolytic enzymes (developed during germination) to hydrolyse the starch granules into simple sugars that have a low water-binding and water-holding capacity. During this stage, the gruel

liquifies, making possible more solids per unit volume, while maintaining a thin consistency (Brandtzaeg et al. 1981). Moreover, absorption from a native porridge with added amylase rich germinated cereal flour (ARF) may be more efficient than a native porridge without ARF.

3. Specific aims:

a) Does the use of a porridge liquefied by amylase rich germinated wheat cereal flour (ARCF) to feed infants and children with acute dysentery lead to increased intake of calorie and nutrient from food compared to (a) the same porridge in a semisolid form without added ARCF and therefore having high viscosity, (b) the same porridge diluted to the same visocity as the experimental porridge with water and therefore having a lower energy density ?

b) Does the feeding of such a porridge have any negative effect on breastmilk intake in breastfed children ?

c) Does the feeding of such a porridge alters the course of illness e.g. diarrhoea duration ?

B. RATIONALE / SIGNIFICANCE

The study will assist in the development of an inexpensive weaning food from locally available food components for use in infants and children with dysentery. In addition to the introduction of a suitable energy dense food during a dysenteric illness this formula could also help for educating mothers in appropriate weaning practices.

C. RESPONSE VARIABLES :

Major or primary

1. Quantity of daily food intake (calories and macro-nutrients) and during the total duration of illness from the experimental porridge on a realistic number of feeds per day.

2. Quantity of daily breastmilk intake in breastfed children and during the total duration of diarrhoea (measured by weight difference before and after feeding using a precision balance).

3. Diarrhoea duration.

4. Cumulative stool frequency by day 3 and day 5.

Secondary response variable

5. Acceptance of the experimental porridge by the children and by the mothers.

D. METHODS AND PROCEDURES

I. Eligibility criteria :

1. Children of either sex aged 6 months to 36 months with a history of bloody diarrhoea of less than 5 days (120 hours).

2. Absence of systemic illness(e.g.pneumonia, meningitis etc.).

3. Absence of complications e.g. HUS, severe hypoglycemia, symptomatic hypernatraemia, toxic megacolon etc.

4. Absence of kwashiorkor, marasmic kwashiorkor or severe marasmus.

5. Parents willing to give an informed consent.

II. Sample size estimation :

Three groups of patients will be studied: the experimental group will receive an energy dense porridge liquefied by adding ARF (group 1), one control group will receive same porridge of equal energy density in semi-solid form without ARF (group 2) and another control group will receive the same porridge liquefied by adding water to the same viscosity as the energy dense liquefied porridge in the experimental group (group 3). The sample size is being calculated to detect a difference between group 1 and group 2 in the quantity of calorie and nutrient intake daily and for the total period of diarrhoea and a reduction in breast milk intake if any between the two groups. Exploratory analysis will also be carried out to detect the differences between group 1 and group 3 for the total energy and nutrient intake and impact on breast milk intake.

We expect a 35% increase in total food intake daily in the experimental group. This is based on our unpublished data on food intake from a single meal of energy dense porridge liquefied by adding ARF compared with a single meal of same semi-solid porridge of same energy density in infants aged 6 months to 12 months. The mean quantity of porridge ingested by the group of infants given a energy dense porridge liquefied with AFR was 41 gms and the mean intake in the control group receving a semi-solid porridge of same energy density was 26 gms. With a standard deviation of 20 the sample size to detect the difference at 5% level of significance and with a power of 80% was 28 in each group.Therefore the total sample size for the three groups is 84.

To this we add 15 for deviated course and the total is 99. For comparison between group 1 and group 3 we note that a 17% porridge of rice needed to be diluted to 60% by adding water to the native porridge to make it similar in viscosity to the liquefied porridge in the experimental group. We expect that the intake from this liquefied porridge in group 3 will be at best the same as the intake from the experimental porridge liquefied by adding AFR. Therefore the equivalent amount of the diluted porridge consumed will be about 24.6 gms in group 3 compared to 41 gms in group 1. With a standard deviation of 20 the sample size in each group is 24 i.e. a total of 72 for the three groups.

In a recent (unpublished) study of shigellosis in this age group , the cumulative stool frequency by day 3 was 50 (SD=30); we like to detect an increase in frequency by 30% i.e. to 65. The sample size for each group (at 5% significance and 80% power) is 64; total sample size is 192 (in 3 groups).

III. Enrollment of subjects :

Patients will be enrolled from the triage area of CRC (treatment centre) of ICDDR,B. Children fulfilling eligibility criteria and attending between 8 am and 12 noon on week days will be considered for inclusion into the study. Not more than 3-4 patients will be recruited each week to enable research staff to carry out all specified activities. Written informed consents will be taken before entering the patient into the study.

IV. Baseline examination :

A history will be obtained and physical examination will be carried out to determine the subject's eligibility for inclusion in the initial trial and to collect relevant data before begining the study that would allow, (a) comparison of the groups after randomization and (b) description of the study population to determine whether the results obtained can be compared with those from other trials. The history and examination will include :

- identification of patients;
- description of symptoms prior to admission and their duration;
- details of any treatment given for the illness;
- a description of feeding status prior to admission and prior to illness;
- a description of the stool prior to admission;
- results of physical examination including state of hydration and fever;
- anthropometric measurements (recumbent length, body weight, mid upper arm circumference, triceps skin fold thickness and tibial length);
- laboratory tests;

The above informations will be recorded on predesigned and pretested forms (Annex 1).

V. Informed consent:

If the patient is found to be eligible for inclusion into the study an informed consent will be obtained (Bangla consent form attached) from the gurdian. The consent form in simple words explains in addition to the antibiotic therapy that a diet treatment will be randomly allocated, the length of stay in the hospital, samples that will be investigated in laboratory e.g., stool, blood and urine. In addition a indication that the patient is free to withdraw from the study at any time and will still receive the standard treatment for his/her illness. The consent will be administered by the PI and then will be witnessed by another staff member. From the third day of hospitalization patients attendant may receive appropriate compensation for the wage loss.

VI. Allocation to treatment groups (Randomization) :

The subjects will be randomly allocated to treatment groups using methods that avoid bias. A randomisation (stratified) code will be prepared using random permuted blocks with a variable block length. The randomisation list will contain more subjects than the estimated sample size to allow for patients that leave the study prematurely. After the randomisation code has been prepared, individual patient assignments clearly typed (on a piece of paper), corresponding with the master randomisation list, will be placed in a series of sealed envelopes serially numbered to correspond to trial numbers. After each patient is selected, next envelope in order of trial number (i.e. in numeri-

cal sequence) will be opened to determine the treatment assignment; thus the investigator will not know the order of randomisation and will be unable to predict the next assignment.
Master randomisation list and sealed envelopes will be prepared by a responsible and appropriately trained person who is not otherwise associated with the study and will be kept safely in two places. The randomisation list will not be accessible to persons in charge of recruiting patients or responsible for observing and recording outcome variables.

VII. Standared case Management

No deviation from routine case management of the treatment centre of CRC will take place except for the type of food offered and that the number of feeds will be standardised.

1. The antibiotic routine of the centre will be used; the first line drug at present is nalidixic acid and the patient will start on nalidixic acid after obtaining stool and rectal swab for culture; if the patient does not respond by day 3 then the drug will be changed to the second line drug i.e.,pivmecillinam (Selexid) or according to the sensitivity of the organism.

2. Rehydration and maintenance of hydration will be carried out with oral rehydration solutions but if necessary intravenous hydration will be done as and when required (as standard hospital practice).

3. Breastfeeding will be continued (the babies will be weighed before and after breastfeeding); standardised feeds will

be offered; four meals of the assigned porridge will be offered in 24 hours; each time porridge will be offered ad lib for a period of one hour; infants and children who are not breastfed will receive milk feeds and an isocaloric milk mixture will be given to an amount of 500 ml per day divided into four feeds;

4. Appropriate treatment for any complications during study will be carried out according to the routine of the centre; if assigned treatment protocol i.e. dietary regime cannot be carried out at certain point due to complications then the data collection will continue as far as is practicable on these patients.

VIII. Withdrawals from the study:

If a patient leaves the hospital before the end of the study, data upto the point of leaving will be considered in the analysis. If a patient develops complications e.g. HUS (who may require transfer to another hospital), paralytic ileus, septicemia, pneumonia, meningitis, severe hypoglycemia/hyponatremia, a patient requiring exclusive parenteral fluid /nutrition management for any reason , which prevents the planned treatment to continue, the patient will be considered as deviated from the study. Data upto the period of deviation will be included in the analysis.

IX. Diet:

a) Study group: A porridge (composed of rice or rice + lentil powder) liquefied by amylase rich germinated wheat cereal flour (ARCF) will be used. The diet will be pretested in a representative sample of patients with acute dysentery in two

age groups : 6 months to 12 months and 13 months to 36 months.

b) Two Control groups: The same porridge (composed of rice or rice + lentil powder) in a semisolid form without added ARCF (Group 2) and the same porridge diluted to the same visocity as the experimental porridge with water and therefore having a lower energy density (Group 3) will be used. Intake will be measured by weight.

X. Organization of the trial:

Patients will be selected from those attending the outpatient unit and admitted to Research Ward II if they fulfill the admission criteria. The PI with the assistance of two co-investigators, will take care of the patients. Eight hourly evaluation will be recorded on a predesigned form. Patients will be admitted from among those seen in the morning upto 11 am to enable a convenient 8-hourly schedule and facilitate recording of relevant events. Diet will be prepared in the metabolic kitchen both for controls and study patients. A full time senior research assistant will be assigned to supervise diet. A pilot phase will be conduced to standardize procedures.

Patients will be followed-up fort nightly up for a period of one month after discharge . During follow-up all anthropometric measurements and BIA will be repeated.

XI. Facilities and patient populations :

Patients will be studied at the metabolic ward of the Centre. The metabolic diet kitchen will be responsible for prepar-

ing the diets under the supervision of the weaning food laboratory.

XII. Methods for response variables

1. Intake of porridge will be measured by pre-weight containers before and after feeding. Total intake of porridge per day and during the whole illness will be computed by combining these measurements. Eight-hourly evaluation will be recorded on a predesigned and pretested form.

2. The number and frequency of stool motions and the presence or absence of blood in the stool will be recorded 8 hourly. Cessation of diarrhoea will be based on consistency of the stool (soft/formed), less than 3 stools in 24 hours and absence of visible blood and/ mucous in the stool.

XIII. Data collection and analysis :

Data forms will be entered in a microcomputer using a data entry template. The pre-intervention data will be summarised and compared among the groups. The study group will be compared with control group 1 for major response variables. Significance tests will be carried out using standared parametric tests for quantitative outcome variables. The distribution of data will be examined for validity of such tests and if necessory appropriate transformations will be carried out before conducting the tests. Otherwise non-parametric equivalents will be used for comparing the two groups. Exploratory analysis will also be carried out by the study group with control group 2 for the same outcome measurements.

Summary of procedures:

Following is the summary of procedures to be done during the study period.

On admission :

1. History and physical examination,
2. Anthropometry : Body weight, Height, MAC, SKFT, Tibial length.
3. Bioelectrical Impedance Assay (BIA)
4. Stool - Microscopic examination.
   - Culture for Shigella
5. Urine - analysis
6. Blood - Hb%, HCT, TC, DC, PC glucose (R)
   - Culture
   - Serum Electrolytes, Serum creatinine, Serum Total protein.
   - Plasma Sp. Gr., Serum Albumin, Retinol binding protein (RBP), Pre-albumin.

Day - 1:

1. Anthropometry : Body weight, Height, MAC, SKFT, Tibial length.
2. Bioelectrical Impedance Assay (BIA) & BIA

Day - 3:

1. Anthropometry : Body weight, Height, MAC, SKFT, Tibial length.
2. Bioelectrical Impedance Assay (BIA)

Day -5:

Stool - Microscopic examination

- C/S for Shigella

Blood - Hb%, HCT, TC,DC, PC, Glucose (R)

- Serum electrolyte, Serum Creatinine, Serum Total protein.

- Plasma Sp. gr., Plasma Albumin, RBP.

- Anthropometry : Body weight, Height, MAC, SKFT, Tibial length.

- Bioelectrical Impedance Assay (BIA)

Day -9:

1. Anthropometry : Body weight, Height, MAC, SKFT, Tibial length.
2. Bioelectrical Impedence Assay (BIA)

Day - 10

Stool - Microscopic examination

- C/S for Shigella

Blood - Hb%, HCT, TC,DC, PC, Glucose (R)

- Serum electrolyte, Serum Creatinine, Serum Total protein.

- Plasma Sp. gr., Plasma Albumin, RBP.

- Body weight, Height, MAC, SKFT, Tibial length.

- Bioelectrical Impedence Assay (BIA)

8 hourly after admission :

- Stool frequency and approximate volume (using diapers).
- Urine frequency and approximate volume (using PUC).
- Vomitus
- Calorie intake (by dietitian and /P.I)

Daily after admission : - Body weight

REFERENCES:

1. Black, R.E., Brown, K.H., Becker, S. Effects of diarrhoea associated with specific enteropathogens on the growth of children in rural Bangladesh. Pediatrics, 73;799-805,1984.

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5. Salam, M.A., Bennish, M.L. Treatment of shigellosis 1. Randomized Double Blind Trial of Nalidixic Acid in Childhood Shigellosis. J Paed. (in press).

6. Ulf Svanberg. Dietary bulk in weaning foods and its effects on food and energy intake. Proceedings of a workshop held in Nairobi, Kenya,12-16 October 1987.

7. Tara Gopaldas, Pllavi Mehata, Chinnamma John , Bulk reduction of Traditional Indian Gruels. Proceedings of a workshop held in Nairobi, Kenya,12-16 October 1987.

8. Rose P. Kingamono, Effect of food consistency on nutrient intake in young children. Proceedings of a workshop held in Nairobi, Kenya,12-16 October 1987.

CONSENT FORM

Your child is suffering from blood dysentery. It has been shown in different studies that. due to profuse loss of blood, mucus and high fever, children can develop malnutrition, edema and weight loss. The children are also susceptible to recurrent infection. Most of the patients develop anorexia so they are unable to maintain their calorie. To counteract this problem we are investigating whether a energy dense porridge of rice or rice plus lentil liquefied with added amylase rich germinated wheat cereal flour is helpful to improve the nutritional status during acute stage of disease. If you agree to participate into the study, your child will have to stay in the hospital for 10 days. During this time your child will be treated with appropriate antibiotics. Beside this your child will be fed with either (a) porridge liquefied by amylase rich germinated wheat cereal flour, (b) the same porridge in a semisolid form without ARCF,(c) the same porridge diluted to the same viscosity as the experimental porridge with water. Stool, urine and 3 ml of blood will be taken for investigation on admission and 2 ml of blood on day 5 and day 10. You will have to bring your child fortnightly, twice for a follow-up .

You may withdraw your child from the study anytime and proper care will not be altered by that. If you agree please sign or give a thumb impression.

Investigator	Witness	Guardian

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. Shigellosis leads to adverse nutritional consequences. Restoring/maintaining adequate nutrition during acute phase and after is an attractive strategy for prevention of malnutrition.

2. Children 6 months to - 36 months of age suffering from shigellosis will be fed either a (a) porridge liquefied by amylase rich germinated wheat cereal flour, (b) the same porridge in a semisolid form without ARF,(c) the same porridge diluted to the same viscosity as the experimental porridge with water and will be compared for nutritional outcome.

3. A detail medical history and clinical information will be recorded on day of admission. Stool, urine, 3 ml blood will be taken on admission and 2 ml of blood will be drawn on day 5 and day 10.

4. The patients will be randomly allocated to 3 dietary groups. All data will be recorded, computerized and analysis will be done with appropriate statistical test.

5. Signed informed consent will be obtained from parents or legal guardians prior to enrolment to the study.

6. Each study patient will get best possible care available in our centre. If the study is successful, it will enable us to formulate early dietary intervention in a realistic way to counteract post-shgiella malnutrition in children.

OUTLINE OF THE PROJECT

CONTROLLED TRIAL OF AN ENERGY DENSE PORRIDGE OF RICE OR RICE PLUS LENTIL LIQUIFIED WITH ADDED AMYLASE RICH GERMINATED WHEAT CEREAL FLOUR IN CHILDREN AGED 6 MONTHS TO 36 MONTHS WITH ACUTE DYSENTERY (i.e., BLOODY DIARRHOEA)

Shigellosis is a major cause of morbidity in developing countries like Bangladesh. It leads to malnutrition, marasmus, kwashiorkor, growth faltering, recurrent infection which increases the mortality of affected population particularly children. So nutritional intervention at the start of the infection/disease process may alter the outcome by reducing morbidity and mortality.

Sixty four patients aged 6 months to 36 months of both sexes in three groups will be selected for study who will attend the outpatient department of Clinical Research Center with a history of bloody mucoid diarrhea of < 5 days duration , and who have >20 pus cells/hpf on microscopic examination of stool. Patients with complicating illness will be excluded from the study. On admission, prior to treatment and nutritional intervention all patients will have two stool cultures , once urine analysis , and one blood culture , chest X-ray if required , and a complete blood count, blood chemistry including total protein, serum albumin , and retinol binding protein will be determined . Patients will be hospitalized for a study period of total ten (10) days. Stool culture , blood count and

chemistry including total protein , serum albumin, retinol binding protein and prealbumin will be repeated on day 5 and day 10. Blood cultures and other tests will be repeated if indicated . Study group will be offered a porridge liquefied by amylase rich germinated wheat cereal flour, control group will be offered either (a) the same porridge in a semisolid form without ARCF, or (c) the same porridge diluted to the same viscosity as the experimental porridge with water. Patients will be followed -up for a period of one month fortnighyly after discharge.

Outcome will be judged by clinical and nutritional improvement. Clinical cure will be judged by improvement in consistency of stools, decrease in and frequency of stool motions, resolution of fever, absence of blood and mucous in stool tenesmus and abdominal cramps. Nutritional improvement will be judged by weight gain , total protein, albumin, RBP assessment and Bioelectrical Impedance Assay (BIA).

INTERNATIONAL CENTER FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH
ARF Study
Clinical Form

Patient's Name | Hospital #

Admission Date | Study #

Admission Time | Age in months

Sex | 1=male | 2=female | Family members

Residence | 1=Dhaka | 2=Tongi | 3=Joydebpur | 4=Gingira | 5=Others

Neighbourhood illness | 1=yes | 2=no | Family illness | 1=yes | 2=no

Duration of bloody diarrhoea (hrs.)

Number of stool motions in last 24 hours

Stool colour | 1=yellow | 2=brown | 3=green | 4=whitish

Stool consistency | 1=watery | 2=loose | 3=Semisolid

Stool character | 1=mucoid | 2=bloody | 3=1+2

Vomiting | 1=yes | 2=no | Duration of vomiting (hrs.)

Number of vomiting last 24 hours | Anorexia | 1=yes | 2=no

Duration of anorexia (hrs.) | Abdominal pain | 1=yes | 2=no

Duration of abdominal pain (hrs.) | Chill | 1=yes | 2=no

Rigor [1=yes | 2=no] Fever [1=yes | 2=no]

Duration of fever (hrs.) [ ][ ][ ]

Last urine passed before admission (hrs.) [ ] Thirsty [1=yes | 2=no]

Tenesmus/straining [1=yes | 2=no]

Duration of tenesmus/straining (hrs.) [ ][ ][ ]

Rectal prolapse [1=yes | 2=no] Degree of prolapse [1 | 2 | 3]

Duration of prolapse (hrs.) [ ][ ][ ]

H/O FEEDING BEFORE ILLNESS

Breast milk [1=yes | 2=no]

Formula [1=yes | 2=no]

cow's milk [1=yes | 2=no]

Semi-solid [1=yes | 2=no]

solid foods [1=yes | 2=no]

FEEDING IN LAST 24 HOURS

Breast milk [1=yes | 2=no]

Formula [1=yes | 2=no]

cow's milk [1=yes | 2=no]

Semi-solid [1=yes | 2=no]

solid foods [1=yes | 2=no]

Outside therapy [1=ampi | 2=SXT | 3=negram | 4=fura | 5=cephal | 6=others]

H/O Immunization :

DPT & polio [1=1dose | 2=2dose | 3=3dose] Measels [1=yes | 2=no]

BCG [1=yes | 2=no] Body weight (kg) [ ][ ].[ ][ ][ ]

Length (cm) [ ][ ].[ ] MAC (cm) [ ][ ].[ ]

Triceps skin fold thickness (mm) [ ][ ].[ ]

Definations

1. Duration of diarrhoea after admission : The in hours from initiation of the study treatment until passage of the last soft stool without blood and / mucus.

2. Stool output : The weight of stool in grams per kg of admission body weight expressed by time period e.g., per 24 hours and for the entire duration of diarrhoea.

3. Diet intake : The volume of diet taken in ml per kg of admission body weight expressed per time period e.g., per 24 hours and for the entire duration of diarrhoea.

4. ORS intake : The volume of ORS taken in ml per kg of admission body weight expressed per time period e.g., per 24 hours and for the entire duration of diarrhoea.

5. Breast milk : Weight of breast milk expressed per time period e.g., per 24 hours and for the entire duration of diarrhoea.

COMPOSITION OF DIETS*
(per 100 ml)

A. FOR YOUNGER CHILDREN (aged 13 mo - 36 mo)

Ingradients	Diet 1	Diet 2	Diet 3
Rice powder	18 g	20 g	20 g
Lentil	6 g	6 g	6 g
Soyabean oil	3 g	3 g	3 g
ARF	2 g	2 g	2 g
Energy (Kcal)	116	116	116
Common salt	0.5 g	0.5 g	0.5 g
Water (ml)	100	100	130
PER	9.3%	9.3%	9.3%
FER	23.2%	23.2%	23.2%
CER	67.5%	67.5%	67.5%

Diet 1 = experimental diet

Diet 2 = energy dense thick porridge

Diet 3 = energy deficient liquid porridge

A. FOR INFANTS (aged 6 mo - 12 mo)

Ingradients	Diet 1	Diet 2	Diet 3
Rice powder	24 g	26 g	26 g
Soyabean oil	3 g	3 g	3 g
ARF	2 g	2 g	2 g
Energy (Kcal)	116	116	116
Common salt	0.5 g	0.5 g	0.5 g
Water (ml)	100	100	130
PER	5.2%	5.2%	5.2%
FER	24.5%	24.5%	24.5%
CER	70.3%	70.3%	70.3%

Diet 1 = experimental diet

Diet 2 = energy dense thick porridge

Diet 3 = energy deficient liquid porridge

* Compositions are calculated as proximate valuses from "Nutritive value of Indian foods" by Gopalan *et al.*

PREPARATION OF ARF (From wheat):

1. The cleaned grains of wheat are steeped in excess eater (about double volume) in a stainless steel tray for 12 h.
2. After 12 hours the wheat grains are drained of water.
3. The steeped grains are then wrapped in moist black clean piece of cotton cloth and germinated for 48 hours at room temperature (~28°C).
4. The germinated wheat grains are spread on filter paper to remove surface moisture and dried for 12 hours under a ceiling fan in a stainless steel tray until dry to the touch. The well germinated wheat grains are then separated from the non-germinated grains manually.
5. The dried grains are again dried in an oven at 50°C for 12 hours.
6. The oven-dried grains with shoots are ground to a fine powder in a laboratory blender. The flour is seived through a local seive (called 'chaluni'). This germinated wheat flour constitutes the ARF.
7. The ARF is stored in polythene bags.

PREPARATION OF RICE GRUEL

1. Boiling the measured amount of rice or rice plus lentil with oil for 20-25 minutes.
2. Stiring the gruel at the later part of boiling with a local wooden stirer (called "ghutuni").
3. Remeasuring the gruel after boiling to get the desired amount.
4. Blending the gruel in case of diet to be prepared for infants.
5. Measure the amount of ARF.
6. Mixing the the ARF with the rice gruel and continuously stiring until the gruel liquifies.
7. The porridge is ready for consumption.

SECTION III - BUDGET

1. PERSONNEL SERVICES		1st year	2nd year
Dr.R.N.Mazumder	NOA (25%)	1872	1872
Dr.I.Kabir	NOC (25%)	2871	2871
Paediatritian	(25%)	6000	6000
Research trainee (Doctor) fellow - 1	(100%)	3000	3000
Data management & Statistics trainee fellow - 1	(100%)	1200	1200
Dietician - GS 5	(75%)	4224	4224
Clerk	(20%)	900	900
Secretary	(10%)	621	621
Aya - 4	(100%)	4800	4800
Data manager GS 5	(25%)	660	660
Trainee laboratory research fellow	(100%)	1500	1500
Lab technician (Wahed 10%,Mujib 10%)	(20%)	1200	1200
Trainee Health Assistant - 3	(100%)	4000	4000
		32848	32848

Hospitalisation

Laboratory :	
Biochemical tests of diets (Viscosity,osmolarity,Energy density etc.)	2000
Stool M/E (300 tests)	600
Stool culture for shigella (200)	600
TC, DC (200)	600
Hct, Sp.gravity (200)	600
Xray, Chest & abdomen (50)	250
	4650

Others

Supplies & materials	3000
Non stock items	1000
Printing & publication	500
Xerox	500
Staff clinic	500
Transport	1000
Telex, fax, postage	500
Medical illustration	500
Data mangement	1500
	8500

Summary

	1st year US$	2nd year US$
Personal	32848	32848
Hospitalization	21000	21000
Laboratory	4650	
Others	8500	
Total	66998	32848
Overhead 30%	20100	9854
Grand total	87098	42702

Controlled trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 6 months to 3 years with acute dysentery (i.e. bloody diarrhoea.

.....

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project	✓		
Adequacy of Project Design	✓	✓	
Suitability of Methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget		✓	
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑ Please see comments re anthropometry and withdrawals
- on level of financial support ☐

I do not support the application ☐

Protocol

Controlled trial of energy dense porridge of rice or rice plus lentil liquified with added amylase rich germinated wheat cereal flour in children aged 6 months to 3 years with acute dysentery.

Comments

The rationale for the above study is well explained. The imprecision of "rice or rice plus lentil" is presumably because the final composition of the diet depends upon results of pilot study.

Diets will be offered 4 times per day for one hour, but the times of offering are not specified; moreover note that 8-hourly records may be organizationally complex when food is offered 4 times (not three times). Protocol should specify recording schedule and feeding schedule. As described one recording schedule has two feeds to cover.

Children are followed up as outpatients at day 14 and 28. What measurements (anthropometry) are made then and should they feature as outcome variables measuring ~~maternal~~ nutritional impact.

Forms are included for on study only. Note that tibial length has been omitted from these forms. Stool frequency per 8 hours is not included on WHO forms; but is required for this study.

Randomization: should randomization be stratified according to whether child is breast-fed. What proportion of the 195 children (65 per group: misprinted as 64 throughout protocol) will be breast-fed. Block lengths may need to be chosen differently for breast-fed / non-breast-fed } strata.

ORS intake: protocol does not specify whether this intake is being measured; could it affect dietary intake, especially of rice-ORS is being used.

Deaths and serious complications: few deaths may be expected in

200 children; at one point in the protocol (p 9-10) allowance is made for one sixth defaulters from protocol (84 increased to 99)
Withdrawal from study and implications for analysis need to be more clearly specified. Unless the child has died anthropometry at day 14 and day 28 should be obtained. Diet may be suspended only if child requires intravenous feeding. Measurement of stool output/frequency may need to be suspended, but measurement of dietary intake should not be. Likewise blood sample at 5 and 10 days should continue to be available, as should measurement anthropometry eg not daily but at 5, 10, 14, 28 days even in children who have complications
Thus: continues diet and measurement of its intake
continue practicable anthropometry (but less frequently)
Outcome variables Anthropometry at 14, 28 days is not mentioned. As far as practicable, anthropometry should mirror intervention study for maximum comparability
Acceptance by mothers and children How is this measured? Discourage measurement of child's diet!
Unclear: what is meant on p8 by stating that daily food intake will be measured on "a realistic number of feeds per day". Specify which feeds and how selected e.g. 1st and last feed per day or what?
Clarify: What is meant on p9 distinction between energy dense porridge and native semi-soluble porridge and native porridge. I assume that the same porridge is meant in all three, just that the additions for fermentation are different?
Sample size From pilot data 41 versus 26 gms, I'd adopt conservative 10 gms target (not least because supervision/encouragement during pilot may be greater than when mean feeds diet to her child during trial)
Thus sample size (when sd = 20 gms), without allowance for withdrawals, is 64 per group; increase to 70 per group for minimal losses. Thus trial size of 195 to 210 covers both moderate dietary intake hoped and 30% decrease (presumable increase on p10 is misprint?) in stool frequency. Which frequency is meant? Total, up to day 3, up to day 5?
Fortnightly follow-up At home or as outpatient ... unexplained. And by whom? Observed standardization?

Review of ICDDR,B proposal entitled, "Controlled Trial of an Energy Dense Porridge of Rice or Rice Plus Lentil, Liquified with Added Amylase Rich Germinated Wheat Cereal Flour, in Children Aged 6 Months to 3 Years with Acute Dysentery (i.e., Bloody Diarrhoea)"

P.I.: Dilip Mahalanabis, M.D.

(2)

General Comments

This proposal describes a randomized, controlled clinical trial of several different dietary regimens for children between six and (47) months of age with acute dysentery. A similar protocol for children with acute watery diarrhea has just been reviewed. Many of the same comments on the watery diarrhea protocol also apply to the proposed studies of dysentery. Therefore, the two reviews should be considered simultaneously.

In addition to the specific comments on the acute watery diarrhea protocol, the study of dysentery should specifically focus on the effects of dietary management on protein metabolism, blood loss, and nutrient balance of those nutrients lost with blood. For example, it would be of interest to compare the change in serum albumin and other shorter half-live serum proteins from admission to day 5 amd day 10 in the different dietary groups. Sample size estimates for these observations should be developed. Likewise, differences in hemoglobin, hematocrit, and indicators of iron status from admission to day 5 and day 10 should be compared by dietary group.

Because the number and frequency of stool motions are critical to outcome variables, further explanation of the data collection methods should be provided. Generally, stool is excreted in cholera cots and the exact number of motions during each eight-hour period are not known. Will the investigators depend on the child's attendant's report of stool number or will study personnel record this information?

During the preparation of malt flour, it has been noted that cyanide accumulates at potentially toxic levels in the germinated grain of some cereals and legumes. Extensive work conducted in Britain (see the publications from the Nairobi, Kenya Workshop on Household Technologies for Improved Weaning Foods) has indicated that most of the cyanide can be recovered from the vegetative portion of the germinated grain. Therefore, the rootlets should be removed from the dried germinated grain before the malt flour is prepared. This has been shown to result in acceptably low cyanide levels in germinated sorghum. It would be advisable to check the concentration of cyanide in the product that will be used in Bangladesh.

No budget was provided with the dysentery proposal so no comments are made in this regard.

Controlled trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 6 months to 3 years with acute dysentery (i.e. bloody diarrhoea.

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
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Quality of Project	✓		
Adequacy of Project Design		✓	
Suitability of Methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget			
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification ☑

- on technical grounds

- on level of financial support ☐

I do not support the application ☐

Signature: Kenneth B. Prosser

Date: 30 April 1990

Name of Referee: Professor J. Waterlow

Position: Professor of California, Davis

Institution: Univ. of California, Davis

INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE
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Banglacesr.

October 14, 1990.

To : Chairman, RRC

From : Dr.R.N.Mazumder, CSD

Subject : Reply to reviewers comments on the protocol entitled " Controlled trial of an energy dense porridge of rice or rice plus lentil liquified with added amylase rich germinated wheat cereal flour in children aged 6 months to 36 months with acute dysentery (i.e.,bloody diarrhoea).

Thank you very much for this opportunity of replying the questions raised by the reviewers . Reviewers have sent an extensive but very useful and constructive review of the protocol. I shall answer the queries separately :

External review - 1.

1. Paragraph - 2 : Diets will be offered at 6 am, 10 am, 4 pm and 10 pm. Dietary and recording schedule will be maintained at 8 hourly intervals.

3. Paragraph - 3 : Body weight, height, MAC, SKFT, tibial length will measured during hospitalization and follow-up and will be compared as outcome variables.

4. Randomization : Stratified randomization in variable block lengths will be done.

5. ORS intake : Rehydration will be according to standard hospital procedure.

6. Deaths and serious complications : As we are excluding any complicated patient for study death is less likely. However, any deviated case will be dealt accordingly.

7. Outcome variables: I could not get the point, however as previously mentioned all anthropometric measurements will be done during follow-up on day 14 and day 28.

8. Acceptance : this will be done by a preset questionnaire as mentioned above.

9. Clarify : It is difficult for a lactating mother who is also involved in household works to remain engaged in frequent feeding for her sick child; this problem could be overcome by less fequent energy dense feeds e.g., 4 which is realistic and practical. Reviewer is right, it was mentioned

without ARF (group 2) and diluted porridge (group 3).

10. Sample size : 192 is a adequate sample size.

11. Follow-up : Patients will be followed-up as outpatients.

External review - 2.

1. Paragraph - 2 : Age of the study population will be from 6 months to 36 months not 47 months. Reviewer suggests a nutrient balance study , which may be done in a subset of population. Other shorter half-life protein (pre-albumin) will be measured. To see the indicators of iron status IBP and Ferritin may be measured if laboratory facilities are available.

2. Paragraph - 3 : Stool frequency will be measured by asking attendant to a metal coin in a slot with each motion. At the time of output (8 hourly) no. of coins will be counted by study nurse.

3. Paragraph - 4 : In our laboratory we have all ready tested germinated wheat flour which doesn't contain any cyanide. This is known to occur with germinated Sorgum, Millet and Casaba but not with Wheat.

4. Paragraph - 5 : I am sorry to know that budgetary section has somehow been omitted during mail.