2

Date 22/7/85

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr Omar Rahman Trainee Investigator (if any) _____

Application No. 85-021P Supporting Agency (if Non-ICDDR,B) _____

Title of Study "A Double Blind Randomized Study to Evaluate Intravenous "DHAKA Solution" with and without 25 gms/liter of Dextrose"

Project status:
- (✓) New Study (Pilot Protocol)
- ( ) 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.

Omar Rahman
Principal Investigator

Trainee

85-021 P
24.7.85

SECTION 1 - RESEARCH PROTOCOL

(Pilot protocol)

1. TITLE: A DOUBLE BLIND RANDOMIZED STUDY TO EVALUATE INTRAVENOUS "DHAKA SOLUTION" WITH AND WITHOUT 25 GRAMS/LITER OF DEXTROSE.

2. PRINCIPAL INVESTIGATOR: Dr. Omar Rahman

CO-INVESTIGATORS: Dr. M. Bennish
Dr. A.N. Alam
Dr. A. Salam

3. STARTING DATE: As soon as possible

4. COMPLETION DATE: 2 months after approval

5. TOTAL INCREMENTAL COST: US $ 4565.92

6. SCIENTIFIC PROGRAM: This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Acting Associate Director, PTWG: _____

Date: 21/7/85

ABSTRACT

Hypoglycemia is a common and potentially lethal complication of diarrhea irrespective of etiology and age of the patient and it may in fact have some association with the intravenous rehydration therapy given to patients. There thus appears to be a need for evaluation of a single polyelectrolyte solution with added glucose which can be used safely and effectively to correct and prevent the hypoglycemia which is associated either with diarrhea intrinsically and /or with the process of rehydration. In addition there is a need to investigate and redocument in a prospective fashion i) the prevalence of hypoglycemia associated with diarrhea and ii) any association with age,type of diarrhea and degree of malnutrition.

We propose a randomized study to evaluate the safety and efficacy of a new intravenous rehydration solution "DS-G" (Dhaka solution + 25g/l dextrose---sodium 133mmol/liter ; potassium 13mmol/liter ; bicarbonate 48mmol/liter (derived from acetate) ;

chloride 98mmol/liter ; and glucose 139mmol/liter;) in comparison to"DS" the existing Dhaka solution.

Subjects selected for this study will be male patients of all ages who come to the International Centre for Diarrheal Disease Research, Bangladesh "Treatment Centre" in Dhaka with diarrhea and need intravenous rehydration therapy. These patients will then be randomly assigned to one of two groups i) a group receiving DS with no added glucose and ii) a group receiving DS-G(DS + 25g/l dextrose). Prior to the onset of intravenous therapy a complete history and physical exam will be done on all patients with special attention being placed on age, weight, degree of malnutrition. In addition blood will be drawn for serum electrolytes, creatinine, glucose and osmolality. Subjects will also provide stool for diagnostic evaluation. All patients will receive intravenous therapy according to a standard protocol (18) for a minimum of four hours during which time no oral supplemental feedings will be given. Once four hours have elapsed oral supplementation will be started. However intravenous therapy will be continued until the patient's hydration status is considered to be adequate according to set criteria (18).

Blood will be drawn for serum electrolytes, creatinine, glucose and osmolality at four hours and at twenty four hours after the onset of intravenous therapy.In addition two successive

four hour urine collections (in the first eight hours of intravenous therapy) will be analyzed for urine glucose, volume and osmolality. A spot urine sample will also be drawn at twenty four hours for urine glucose and osmolality. Stool volume will also be assessed at four, eight and twenty four hours following the onset of intravenous therapy.

Once twenty four hours have elapsed there will be no further laboratory investigations involving the patients. However they will continue to be followed clinically and will remain in the study until they are discharged from the treatment centre. Prior to discharge the total duration of intravenous therapy, the total volume of intravenous rehydration solution and the duration of hospital stay will be recorded for each patient involved in the study.

The two treatment groups will be assessed and compared according to the following criteria: i) degree of hypoglycemia in both groups, ii)extent of glucosuria and concomitant osmotic diuresis (in the DS-G group) and iii) duration required for euhydration in both groups.

An analysis will also be made of any association between the degree of hypoglycemia and i)age of the patient, ii)degree of malnutrition, and iii)type of diarrhea, cholera vs non cholera.

OBJECTIVE

To assess the effectiveness of "Dhaka solution" + 25g/l dextrose relative to "Dhaka solution" in treating and preventing hypoglycemia associated with diarrhea.

BACKGROUND

Replacement of water and electrolytes remains the cornerstone of therapy in the treatment of diarrheal diseases. Despite major advances in oral rehydration solutions intravenous rehydration is still the modality of choice in cases of severe dehydration. Although there is a wide spectrum of presentations both in the etiology (cholera vs non cholera) and in the osmolar/sodium status of the patient (hypotonic/hyponatremic vs isotonic vs hypertonic/ hypernatremic)there appears to be justification (from both physiological and pragmatic considerations) for the use of a single polyelectrolyte intravenous solution for the treatment of all cases of diarrheal dehydration (1). One such solution is the so called "Dhaka solution" or "Acetate solution"(2) (sodium 133 mmol/liter ; potassium 13 mmol/liter ; bicarbonate 48 mmol/liter (derived

from acetate) ; and chloride 98 mmol/liter) which has been used very effectively for many years at the International Centre for Diarrheal Disease Research,Bangladesh.

There has been much written in the medical literature about electrolyte problems associated with diarrhea, (hypernatremia, hyponatremia, hypokalemia) but not much attention has been given to hypoglycemia as a complication of diarrhea, even though it has been documented to be a serious problem. The first report of occasional cases of profound hypoglycemia in children with diarrhea both at admisssion and following rehydration was documented by Hirschorn et al in 1966(3).Their study (which was conducted in the period 1963 to 1966 on children with acute diarrhea presenting to the Cholera Research Laboratory (now known as International Centre For Diarrheal Disease Research, Bangladesh) treatment centre in Dhaka Bangladesh) showed that "significant hypoglycemia is a not infrequent, potentially fatal complication of acute infectious enteritis in children in East Pakistan "(3). Cases were reported in association with both cholera and non-cholera diarrhea and there appeared to be no consistent correllation between degree of malnutrition and hypoglycemia.

One of the more significant findings of the above study was that in some children hypoglycemia occurred many hours after

a dequate hydration had been given and any shock had been corrected. In fact in a corresponding pilot study on seventeeen consecutive children admitted with an acute diarrheal illness who were fasted but hydrated with intravenous electrolyte solutions containing 50meq lactate/liter but no glucose, blood glucose (in 9/17) fell below 400 mg/liter after a mean fast of 30 hours (range of 10-48 hours)."In general the fall in glucose was greatest during the period of rapid rehydration. The hypoglycemeic children did not differ from the others in age, weight percentile, degree of dehydration, severity of illness, or amount of lactate received"(3).

The etiology of the hypoglycemia associated with diarrhea remains unclear. The authors of the above study rejected hyperinsulinism, or increased blood ketones as a possible cause as both insulin levels and ketone levels were found to be low or within normal limits.There is an implication that failure of gluconeogenesis, either due to an insufficiency of adrenal hormones or due to hepatic dysfunction may account for the hypoglycemia. However no definite proof is given for these hypotheses.

There have been scattered reports in the medical literature since the study cited above (4,5) but it was not until 1981 that a larger series documenting hypoglycemia as a complication of

diarrhea was reported (6).In this 4 year retrospective study A.M.Molla et al examined the case records of 26,521 patients less than 10 years presenting to the ICDDR,B treatment centre at Dacca with acute diarrhea of different etiologies. They found that at admission approximately one percent (231/26,521) of the children were significantly hypoglycemic(blood sugar below 2.2 mmol/liter). The hypoglycemia seemed to be evenly distributed among children less than ten years and the severity was unrelated to duration of diarrhea.

Perhaps the most significant finding of the "Molla" study was that the case fatality rate for children with hypoglycemia and diarrhea was significantly higher than the overall case fatality rate for that particular type of diarrhea irrespective of etiology or age of the patient.Thus in shigella overall case fatality was 8.3% against 46.2% in shigella associated with hypoclycemia ($p<0.001$). Similarly in cholera overall case fatality was 0.7% against 14.3% in cholera with hypoglycemia.

This report was preceeded in 1979 by M.M.Rahman et al (7) who documented that in patients suffering from diarrrhea of different etiologies and belonging to various age groups, there was a significant drop in serum glucose levels compared to admission serum glucose values four hours following the onset of intravenous hydration. In this particular study the investigators

were comparing the efficacy of two different intravenous solutions, i) "Dhaka" solution" (DS) and ii) "Diarrhea treatment solution"(DTS) { which contains sodium in a concentration of 118 mmol/liter and glucose at 44 mmol/liter or (8g/l) }. While the group receiving DTS (8g/l of dextrose) had consistently higher serum glucose levels at each time interval (4hr, 24hr, 48hr and 72hr) following onset of intravenous therapy their serum glucose values were still significantly lower than their admission serum glucose levels.Thus the addition of 8g/l of dextrose was not sufficient to prevent a marked drop in serum glucose with rehydration.

As mentioned above the etiology of the hypoglycemia associated with diarrheal dehydration is unclear, however there is an intriguing suggestion by Spirer) (8) which implies that the drop in blood glucose post hydration may be secondary to the correction of acidosis.

Given the potentially lethal complications of hypoglycemia in association with diarrhea and the documented marked decrease in serum glucose levels following intravenous hydration of diarrhea patients (3,7) there would appear to be a need to evaluate the efficacy and safety of a single polyelectrolyte-glucose/dextrose intravenous solution in the treatment and prevention of this form of hypoglycemia.

There is also a need to investigate further and redocument in a prospective fashion i) the prevalence of hypoglycemia associated with diarrhea and ii) any association of this form of hypoglycemia with age, degree of malnutrition and type of diarrhea (cholera vs noncholera).

The optimal concentration of dextrose in such a polyelectrolyte solution as mentioned above has not been determined. Various concentrations have been proposed : i) Hirschorn recommended 10 g/litre of dextrose (7) and ii) M. Rahman et al (7) investigated 8g/l of dextrose . The latter amount was however found to be insufficient in preventing the marked drop in serum glucose levels post intravenous rehydration (7).

The amount of dextrose that can be added to an underlying polyelectrolyte solution is limited by concerns about hyperglycemia and glucosuria with resulting osmotic diuresis causing a further degree of obligate renal fluid loss. Given the fact that it is often required to transfuse patients with upto 10% of their body weight within thirty minutes (faster than the glucose can be transported in to the cells) the possibility exists of an osmotic diuresis phenomenon.

The glucose turnover rate for adults is 2mg/kg/min (9) and for infants it is approximately 6mg/kg/min (9). The possibility of an osmotic diuresis phenonomenon can be better appreciated from the following sample calculation:

The rehydration of a 5kg severely dehydrated child (10% dehydration) would require the administration of (10/100 times 5kg) = 500 mls (0.5l) of intravenous fluid containing 25g/l of dextrose over a period of four hours (10). This means the child would receive (0.5l times 25g/l) = (12,500mg/240min) = (52.1 mg of glucose/min). The glucose turnover rate for such an child is (at most 6mg/kg/min times 5kg)= 30mg of glucose/min. Thus the rate of administration of glucose clearly exceeds the glucose handling capacity of the body.

This above theoretical calculation seems to indicate that accepted (10) rates of intravenous fluid administration in diarrhea patients should result (if 25g/l of dextrose is used) in a sharp rise in plasma glucose and consequently a marked increase in filtered glucose concentration in the renal glomerulus.The renal threshold for glucose is 1.6g/l/min (11,12).This means that any glucose in excess of this amount will be only partially reabsorbed and there will be a certain amount of spillage in the urine dragging along with it a concomitant amount of renal water loss . The situation is further exacerbated

once the concentration of glucose in the renal glomerulus reaches 3.3g/l/min (11,12). This represents the absolute reabsorbtive renal threshold for glucose and any glucose in excess of this figure will be totally spilled in the urine, dragging along with it a significant amount of obligate renal water loss.

In contrast to the theoretical considerations mentioned above, Sperotto (13) reported a study in 1977, on twelve well nourished infants with acute diarrhea who were given 1/2 isotonic saline + 25g/l of dextrose at rates exceeding 30ml/kg/hr (i.e. glucose administration rates greater than 12.5 mg/kg/min, far in excess of the 6mg/kg/min handling capacity of infants) where glucosuria was only recorded in 25% of the subjects and was not very significant. In addition there was no significant increase in plasma osmolality.

There is also evidence from experiences in total parenteral nutrition that large amounts of intravenous glucose may be well tolerated (14).

An area of particular concern is that subset of patients with hypernatremia (which fortunately is relatively uncommon in the tropics (1)). As upto 25% of these hypernatremic patients have hyperglycemia on presentation (15,17), the rapid infusion of

large volumes of glucose containing intravenous fluids may be problematic. However Finberg (17) feels that in hypernatremia glucose transport into cells per se is unimpaired (i.e.the elevated plasma glucose level has no osmolal significance) and the problem is the serum sodium concentration. Spirer (8) on the other hand suggests that the hyperglycemia associated with hypernatremic patients may really be a function of their acidosis status and not of their serum sodium concentration as such. As mentioned earlier Spirer's data showing the resolution of hyperglycemia (with resulting frank hypoglycemia in two of his subjects) with adequate base containing hydration has interesting implications as to the causative mechanism of the marked drop in blood glucose post intravenous rehydration documented in earlier studies.

Possible explanations as to why glucosuria may not be a significant problem with rapid intravenous glucose administration in dehydrated diarrhea patients include i)the observation that decreased GFR in severe dehydration may cause the filtered load of glucose to be less than the renal absorbtive threshold. and ii) correction of acidosis (as per Spirer (8)) may cause accelerated transfer of glucose into cells.

Thus a review of the medical literature indicates that while glucosuria and concomitant osmotic diuresis is theoretically a

significant complication of rapid intravenous glucose administration there is not much empirical evidence supporting it. Given that 8g/l dextrose solution was not found to be sufficient to prevent the marked drop in serum glucose levels post intravenous therapy , we have opted arbitrarily to use 25g/l dextrose solution in our study keeping in mind the above theoretical considerations.

We therefore propose a randomized study to evaluate the efficacy and safety of a new intravenous rehydration solution DS-G in comparison with Dhaka solution in the treatment and prevention of hypoglycemia associated with diarrhea. We also propose to investigate and document in a prospective fashion (in diarrhea patients) any relationship that exists between hypoglycemia and age, degree of malnutrition and type of diarrhea (cholera vs non cholera).

SPECIFIC AIMS

To evaluate the safety and efficacy of a new intravenous rehydration solution DS-G (Dhaka solution + 25g/l dextrose) in comparison to DS Dhaka solution in the treatment and prevention of hypoglycemia associated with diarrhea.

Efficacy will be judged by comparing serum glucose levels at 4hrs and 24hrs (following the onset of intravenous therapy) in the two groups and by comparing these levels to accepted normal values.

Safety will be judged by the following criteria :

(1)recording and comparing any clinical manifestations and/or laboratory evidence of hypoglycemia in both groups.

(2)recording and comparing any gross electrolyte abnormalities in both groups.

(3)recording and comparing evidence of increased serum osmolality and in both groups at 4hrs and 24hrs following the onset of intravenous therapy (as a measure of the state of hydration).

(4)assessing the extent of glucosuria and concomitant obligate

renal water loss at 4hrs and at 8hrs by measuring the volume of urine collected (over that particular time period)along with the urine osmolality and urine glucose concentration in that sample. The relevant calculations for the four hour sample are: Minimum urine volume due to osmotic diuresis(minimum obligate renal water loss) ={total amount of glucose in that 4hr collection (in mmoles)} divided by {(theoretical) maximum urine osmolality(1200mmol/liter) } (12)

(5) recording and comparing the duration required for euhydration in the two groups as estimated approximately by serum and urine osmolalities at 4hrs and 24hrs following the onset of intravenous therapy.

PATIENTS AND METHODS

Statistical Analysis:

A total of seventy two patients (36 in the DS group and 36 in the DS-G group) will be studied. This sample size was arrived at as follows.

The primary data will be arranged such that we have four age categories : a) 0-1 b) 2-5 c) 6-14 d) 15 and above. Each age category will be divided into experimental (DS-G) and control (DS) groups with equal numbers of patients in each group. Thus there will be a total of eight groups (two for each age category)

We assume an alpha value of 0.05 and a Beta value of 0.20. We want in each age category, a power of 80% in detecting a difference of 250mg/l in the (true population) mean serum glucose values between the DS and DS-G groups.

n = 2{ [(Zalpha minus Zbeta) sigma]squared } divided by {delta squared}

where:

Zalpha = 0.05.

Zbeta = 0.20.

sigma = pooled standard deviation = standard deviation of DS group = standard deviation of DS-G group = 150 mg/l [historical data (7)]*

delta =(the magnitude of the assumed true difference in the population means of the DS and DS-G groups that we would like to detect) = 250mg/l.

* We are assuming a normal distribution for the sample means of the serum glucose values. We are also assuming that we know sigma (which we have ascertained from previous similar studies).

Using the above formula n(sample size) = 5, for each group (DS or DS-G) in each age category. Thus a minimum of 40 patients are required for a study to satisfy the above conditions.

It should also be noted that the power of detecting a difference of 250mg/l in the true population means of the serum glucose values in the DS and DS-G groups in the total or pooled sample (all age categories combined) is considerably greater than 80%

There are two other statistical associations that we would like to investigate apart from age and hypoglycemia :

i) degree of malnutrition and hypoglycemia-- a comparison would be made ofseverely malnourished patients of all ages receiving DS vs DS-G. A similar comparison would be made for patients of less severe degrees of malnutrition (pooled together) receiving DS vs DS-G.

ii) type of diarrhea (cholera vs non-cholera) and hypoglycemia. Comparisons would be made of all patients presenting with cholera (pooled together) receiving DS vs DS-G. A similar comparison would be made for non-cholera diarrhea patients.

Due to the difficulty of getting adequate number of malnourished and cholera patients in each individual age category it was decided to study these associations in the pooled sample. To increase the probability of detecting valid statistical associations between malnutrition and hypoglycemia and type of diarrhea and hypoglycemia it was arbitrarily decided to increase the pooled sample size to slightly less than double the minimum pooled sample size calculated above.

Thus a total of seventy two patients will be studied .

STUDY DESIGN:

Inclusion Criteria

Only patients who meet all of the following criteria will be entered into the study:

Any male patient (regardless of age) who comes to the ICDDR'B Dhaka hospital treatment centre and is considered by the medical housestaff/nurse to need intravenous rehydration treatment will be included in the study provided that he has given his written consent(as documented by a witness) to participate in the study or in the case of a patient under 18 years of age the parent or legal guardian has given consent.

For the sake of practicality we have chosen only male patients, as we will be measuring urine volumes,osmolalities,and glucose concentrations with a fair degree of precision. In our experience urine collections tend to be somewhat unreliable in female patients due to admixture with stool.

Exclusion Criteria

Patients with the following complications will not be

included in the study:

i)any form of abnormal mental status.

ii)convulsions.

iii)any other complicating illness apart from diarrhea (e.g. pneumonia).

iv)any history of diabetes.

v)any history of receiving intravenous fluid just prior to admission.

In actuality any seriously ill patient on presentation to the ICDDR'B Dhaka hospital is automatically triaged to the in-patient ward or the intensive care unit. The treatment center is designed to treat only uncomplicated cases of diarrheal dehydration. Thus the above exclusion criteria will automatically be satisfied by almost all patients in the treatment center.

Exclusion Criteria During The Course Of The Study

Patients who i) develop any of the above mentioned complications

(cf. i) ii) iii) of the Exclusion Criteria) during the course of the study or ii) have not adhered to the study schedule and procedures as defined by the protocol (e.g. refuse blood drawings) will be excluded from the study. The reason for the exclusion of any patient will be duly recorded.

SCHEDULE OF STUDY PROCEDURES

1)Once the patients have met the selection criteria they will be transferred to the study ward and assigned(according to a randomization code)to receive one of the following intravenous rehydration regimens:

i)Dhaka solution (DS) [sodium 133mmol/liter; potassium 13mmol/liter; bicarbonate 48mmol/liter (derived from acetate) and chloride 98mmol/liter;] or

ii)Dhaka solution + 25g/l of dextrose (DS-G) [as above with the addition of Glucose 139mmol/liter]

The solutions will be labelled A and B and neither the patient nor the investigator will know the identity of the intravenous solution used for any specific patient.

2)Prior to starting intravenous therapy a thorough history and physical exam will be completed with special attention being given to (i) age, (ii) weight, (iii) degree of dehydration, (iv) degree of malnutrition and (v) duration of diarrhea.

The degree of malnutrition will be assessed by using two different criteria; i) arm circumference and ii) weight/height(to

avoid any discrepancies due to weight loss secondary to acute diarrhea, we will use 24hr post admission weight,i.e after the patients have been adequately rehydrated). Arm circumference is in any case probably the better of the two indices as it may be a better indicator (than weight/height) of fat reserves and potential for gluconeogenesis [an important etiological consideration in hypoglycemia associatied with diarrhea (3)].

The degree of dehydration will be assessed using standard clinical criteria (10).

3)In addition prior to starting intravenous therapy blood (3mls) will be drawn for serum electrolytes,glucose,osmolality and creatinine.

4)Patients will also provide stool for i)bacteriological cultures for V.Cholerae, Shigellae, Salmonellae, Toxigenic E-coli ii)Elisa testing for Rotavirus. and iii) stool microscopy.

5)All patients will receive intravenous therapy for a minimum of four hours and following this period for as long as is considered necessary. A standard protocol will be followed in this regard (18).During this four hour period the patients will not receive any supplemental oral feeding. However once this initial four hour period is completed patients will receive whatever oral

supplementation is routinely administered in the treatment centre.

6)Four hours after the onset of intravenous therapy the following investigations will be carried out :

i)all patients will have blood (1ml) drawn for serum electrolytes, creatinine, glucose and osmolality.

ii)urine output for the preceeding 4hrs will be analysed for urine volume and urine glucose concentration. In addition a spot sample at 4hrs will be analysed for urine osmolality.

iii) all patients will have their stool output upto that point recorded.

7)Eight hours after the onset of intravenous therapy the following investigations will be carried out:

i)Urine output for the second of two succesive four hour collections) will be collected and analyzed for urine volume and urine glucose concentration. In addition urine osmolality will also be measured on a spot sample at 8hrs.

ii)Stool output upto this point will also be measured.

8)Twenty four hours following the onset of intravenous therapy the following investigations will be carried out on all the patients in the study :

i)Blood (1ml) will be drawn for serum electrolytes, creatinine,glucose and osmolality.

ii)a spot urine sample for glucose concentration and osmolality will be collected

iii)Total stool output upto that point will be recorded.

iv) "Rehydrated weight" will be recorded.

9)Once the above mentioned investigations are completed there will be no further laboratory investigations involving the patients and they will be transferred back to the General ward / Treatment center. The patients however will be followed clinically and will remain in the study until they are discharged from the treatment centre. Prior to discharge, the following parameters will be recorded for each patient involved in the study:

i)total duration of intravenous therapy.

ii)total volume ofintravenous solution received.

iii)total duration of hospital stay.

We have decided to provide some type of positive incentive

to the participants in the study. Thus all patients enrolled in the study will be screened 24hrs post admission for anemia by means of a "spun hemotocrit" and any patient found to be significantly anemic will be appropriately treated.

SUMMARY OF DATA COLLECTION

0hrs----- i)history and physical exam (age,weight,degree of malnutrition) ii)Serum electrolytes, glucose, creatinine and osmolality (3mls of blood).

4hrs----- i)Serum electrolytes,glucose,creatinine and osmolality (1ml of blood) ii)Urine collection for the preceeding 4hrs to be analysed for urine volume and glucose concentration. iii)In addition spot urine sample at 4hrs for urine osmolality. iv)Stool volume.

8hrs----- i)Urine collection for the preeceding 4hrs to be analysed for urine glucose and volume. ii)In addition spot urine sample at this time for urine osmolality. iii)Stool volume.

24hrs-----i)Serum electrolyltes,glucose,creatinine and osmolality (1ml of blood).
ii)Spot urine sample for glucose concentration and osmolality.
iii)Stool volume. iv) rehydration weight

Misc.-----i)Stool (one sample) for bacteriological cultures/Elisa test and microscopy
ii)Total duration of intravenous therapy.
iii)Total volume of intravenous solution received.
iv)Duration of Hospital stay.

Positive incentive--- Blood for "spun hematocrit" 24hrs post admission.

BIBLIOGRAPHY

1)HIRSCHORN, N. The treatment of acute diarrhea in children: An historical and physiological perspective.The American Journal of Clinical Nutrition,33:637-663 (March 1980).

2)GREENOUGH, W.B. III. Vibrio Cholerae :In: Principle and Practice of Infectious Diseases, edited by MANDELL, G.L., DOUGLAS, G.R., BENNETT, J.E., ch. 172, pp 1677-1678, John Wiley and Sons Inc.,(1979).

(3)HIRSCHORN, N., LINDENBAUM, J., GREENOUGH, W.B., ALAM S.M. Hypoglycemia in children with acute diarrhea.Lancet,2 : 128-132 (1966).

4)JONES, R.G. Hypoglycemia in children with acute diarrhea. Lancet 2 : 643 (1966).

5)CHALMERS, R.A., LAWSON, A.M., WHITELAW, A., PURKISS, P. Twin siblings with a Reye's like syndrome associated with an abnormal organic aciduria, hypoglycemia,diarrhea and vomiting with close similarities to Jamaican vomiting sickness. Pediatric Research 14 : 1097-1103 (1980).

6)MOLLA, A.M., HOSSAIN, M., ISLAM,R., BARDHAN, P.K., SARKER, S.A. Hypoglycemia: A complication of diarrhea in childhood. Indian Pediatrics 18 : 181-185 (March 1981).

7)RAHMAN, M.M., MAJID, M.A., MONSUR, K.A. Evaluation of two intravenous rehydration solutions in cholera and non-cholera diarrhea. Bulletin of The World Health Organization, 57 (6) 977-981 (1979).

8)SPIRER, Z., BOGAIR, H. Blood sugar in infants with diarrhea. Lancet 2 : 1311, (1970).

9)MCLAREN, N.K. Nutritional considerations in the etiology and treatment of hypoglycemia :In: Textbook of Pediatric Nutrition, edited by Robert M. Suskind, p.460, Raven Press Books, Ltd. (1979).

10)Management of the dehydrated patient :In: A Manual For The Treatment Of Acute Diarrhoea, pp.8-12, WHO/CDD/SER/80.2 REV. 1 (1984).

11)BERL, T., SCHRIER, R.W. Renal function in pregnancy :In: Renal and Electrolyte Disorders, edited by R. W. Schrier, pp. 473-474 (1976).

12)WEIL, W.B., BAILIE, M.D. Volume Disorders :In: Fluid & Electrolyte Metabolism in Infants and Children: A Unified Approach., edited by Weil,W.B. and Bailie, M.D., ch.4, pp. 100-102, Grune & Stratton, Inc. (1977).

13)SPEROTTO, G., CARAZZA, F.R., MARCONDES, E. Treatment of diarrheal dehydration. The American Journal Of Clinical Nutrition, 30 : 1449-1450 (September 1976).

14)FILLER, R.M. :In: Textbook of Pediatric Nutrition, edited by Robert M. Suskind, p.350, Raven Press Books,Ltd. (1981).

15)STEVENSON, R.E., BOWYER, F.P. Hyperglycemia with hyperosmolal dehydration in non-diabetic infants. Journal of Pediatrics 77 : 818-822 (1970).

16)HAYCOCK, G.B. :In: Textbook of Pediatric Nutrition, edited by D.S. Mclaren and D. Burman, p 217, Longman Group Limited (1982).

17)FINBERG, L. :In: The Body Fluids in Pediatrics, edited by Winters,R.W. ch. 18, p.349, Boston Little,Brown & Co. (1973).

ABSTRACT SUMMARY

1)Our subject population will be male patients of all ages who need intravenous rehydration therapy. As we will be measuring urine volumes, glucose concentrations and osmolalities with a fair degree of precision,for the sake of practicality we have chosen only male patients. It is our experience that urine collections in female patients tend to be unreliable (due to admixture with stool) in a relatively unmonitored setting such as a busy treatment centre. We appreciate the fact that our conclusions may theoretically have a sex bias. However there is nothing in the available medical literature that indicates any sex related differences with respect to hypoglycemia associated with diarrhea.

2)The only invasive procedure that we will do during the study is blood drawing.The amount of blood (5mls in total for each patient) that will be drawn during the study will pose no risk to the patients.

3)The only possible risk for the experimental (DS-G) group is that due to the rapid infusion of large amounts of glucose rich intravenous fluid an osmotic diuresis phenomenon with its obligate renal water loss may occur. This phenomenon will have

the effect of slightly prolonging the dehydration of the patient and the patient would need a somewhat larger total volume of intravenous fluids.

To safeguard confidentiality and protect anonymity
4)All patients enrolled in the study will be assigned a study number and that number will be used throughout when analysing information collected from such patients.

5)Informed consent will be obtained from the patient or in the case of the patient being below 18 years of age, from the parent or legal guardian. Patients will receive the same level of care (the best available for their condition) regardless of whether they agree to participate in the study or not.
6)A standard medical history and physical examination will be completed at the time of entry into the study.

7)The study will also require the use of hospital records,(which we will record ourselves) stool urine and blood.

8)Each individual patient will receive the best care available for their condition. The major disadvantages are i)that the patients will have some blood drawn which otherwise would necassarily not have been done and ii) that some of the DS-G patients may have a slightly prolonged period of dehydration and receive intravenous therapy for a slightly longer period of time than otherwise required.

These relatively minor and transient inconveniences (at no time will any patient face any significant adverse outcome) need to be weighed against the potential benifits accruing from the information gained in this study. Society will benifit because we will have to opportunity to see if this new intravenous solution can treat and prevent the hypoglycemia associated with diarrhea.

In addition as a positive incentive, all participants in the study will be screened for anemia (by means of a 24hrs postadmission "spun hematocrit"). Anyone found to be significantly anemic will be appropriately treated with iron supplements. As this is not a routine procedure for all patients treated at the treatment center,the participants in the study will get some extra benefit for their cooperation.

DETAILED BUDGET

(1) Personnel Services

Name	Position	% Effort	$
Dr. Omar Rahman	Principal Investigator		00.00
Dr. Micheal Bennish	Co-Investigator	as consultants	00.00
Dr. Ahmed N. Alam	Co-Investigator		00.00
Dr. Abdus Salam	Co-Investigator		00.00

(2) Supplies and Materials

Item	$
Needles,syringes,vials for serum collection	100.00
Urine collection bags	050.00
Intravenous solutions	100.00
Total Costs for Supplies and Materials	250.00

(3)Laboratory Tests

(For one patient who completes the study).

Test	Cost/Test ($)	No.ofTests	Cost($)
Serum Electrolytes	2.77	3	008.31
Serum Creatinine(reg)	2.13	2	004.26
(extra)	3.13	1	003.13
Serum Glucose	1.58	3	004.74
Spun Hematocrit	0.18	1	000.18
Serum Osmolality	2.50	3	007.50
Urine Osmolality	2.50	3	007.50
Urine Glucose	1.58	3	004.74
Stool Cultures :			
Vibrio Cholera	1.87	1	001.87
Salmonella/shigella	2.75	1	002.75
E-coli for ST/LT	1.50	1	003.00
Rotavirus/Elisa	2.50	1	002.50
Stool Microscopy	0.13	1	001.13
Total Lab. costs for one patient			051.61
Total Lab. costs for seventy two patients			3715.92

BUDGET SUMMARY

(1)Personnel Services	No cost
(2)Total costs of supplies and materials	$ 250.00
(3)Total Lab. costs for seventy two patients	$3715.92
(4)Equipment	No cost
(5)Patient Hospitalization	$0600.00
(6)Outpatient Care	No cost
(7)ICDDR´B Transport	No cost
(8)Travel & Trasnsportation of Persons	No cost
(9)Transportation of Things	No cost
(10)Rent,Communication & Utilities	No cost
(11)Information Services	No cost
(12)Printing and Reproduction	No cost
(13)Other contractual Services	No cost
(14)Construction,Renovation,Alteration	No cost
Total Cost For SEVENTY TWO Patients	$4565.92

ENGLISH CONSENT FORM

You are/ (your child is) suffering from diarrhea. The diarrhea has caused you/(your child) to lose a great deal of salt water from the body.You need/(your child needs) to get this fluid replaced through the intravenous route as quickly as possible.

Sometimes in patients suffering from diarrhea the level of sugar in the blood can fall to a very low level and this can be very dangerous for the patient. Unfortunately it is difficult to predict who will be affected.

We want to find out whether we can prevent the blood sugar from falling in patients with diarrhea by adding some sugar to the intravenous solution that they normally receive.

If you agree we will include you/(your child) in our study.

If you/(your child) is included in this study we will take a detailed history from you concerning your/(your child's) medical problems and will examine you/(your child) thoroughly and record the findings. We will then take a small amount of blood (3ml) and stool for different investigations. You /(your child) will then receive the intravenous fluid that you need/(he needs) to replace

the fluid and electrolytes/(water & salt) that yourbody/(hisbody) has lost. The only difference from normal procedure is that instead of receiving the regular intravenous solution used in the treatment centre, you/(your child) may receive the regular intravenous solution with a certain amount of added sugar.

You/(your child) will receive the intravenous solution for atleast four hours and after that for as long as is considered necessary to replace the fluid your body/(your child's body) has lost. Four hours after starting intravenous therapy we will take a small amount of blood (1ml) for different investigations.

Four and eight hours after starting intravenous therapy we will collect any urine and stool you have/(your child) has produced for other investigations.

The next day again a small amount of blood (1ml) and some urine will be taken from you/(your child) for different investigations. and the 24hr stool output will be recorded.
The small amounts of blood taken will not cause any harm to you/(your child).

You/(your child) will remain in the study until you are/(your child is) discharged from the treatment centre. All appropriate measures will be taken to treat you/(your child). During the study you/(your child) will not get any physical injury other

than a little pain at the time of drawing blood.

Your consent to include you/(your child) in this study will help us to find the most effective treatment for this condition. In addition as an extra benefit for participating in the study, you/(your child) will be screened for anemia and if found to be anemic will be treated appropriately.

You are free to withdraw yourself/(your child) from the study at any time you want. Even if you do not give consent for the study, you/(your child) will get the usual/appropriate treatment for this condition.

We will let you know the reports of the investigations done if and when you so desire.

Signature of the Investigator----------

Signature of Witness ----------

Signature/(thumbprint) of patient/legal guardian or parent

Date----------

সম্মতি পত্র

আপনি/(আপনার রোগী) উদরাময় ("ডাইরিয়া") রোগে ভুগছেন/(ভুগছে)। এই রোগের ফলে আপনার/(আপনার রোগীর) দেহ থেকে প্রচুর পরিমাণ লবন এবং পানি বের হয়ে গেছে। যততাড়াতাড়ী সম্ভব সেলাইন ইনজেকশনের মাধ্যমে এই হারান লবন এবং পানি দেহে ভরে দিতে হবে।

এইরোগে কোন কোন রোগীর রক্তে শর্করার পরিমান মারাত্মক ভাবে কমে যেতে পারে। এই অবস্থাকে "হাইপোগ্লাইসিমিয়া" বলা হয়। দুর্ভাগ্য বসত কোন ডাইরিয়া রোগী "হাইপোগ্লাইসিমিয়ায়" আক্রান্ত হবেন বলা শক্ত।

আমরা গবেষনার মাধ্যমে দেখতে চাই, ডাইরিয়া রোগীদের সাধারনত যে সেলাইন ইনজেকশন "এসিটেট" দেওয়া হয় তার সঙ্গে কিছুটা শর্করা মিশিয়ে দিয়ে এই "হাইপোগ্লাইসিমিয়ার প্রতিরোধ করা যায় কি না।

আপনার সম্মতি থাকলে আপনাকে/(আপনার রোগীকে) আমরা গবেষনার জন্য ভর্তি করবো। ভর্তির পর আপনার/(আপনার রোগীর) রোগের ব্যাপারে আপনাদের থেকে তথ্যাদি গ্রহন করা হবে, আপনার/(আপনার রোগীর) বিস্তারিত পরীক্ষা করা হবে, এবং তা লিপিবদ্ধ করা হবে। এরপর আপনার/(আপনার রোগীর) থেকে সামান্য পরিমান রক্ত (৩ml) এবং মল বিভিন্ন প্রকার পরীক্ষার জন্যে নেওয়া হবে। আপনাকে/(আপনার রোগীকে) তখন অনুতপক্ষে চার ঘন্টা ধরে সাধারন স্যালাইন "এসিটেট" অথবা শর্করা যুক্ত সেলাইন "এসিটেট" ইনজেকশন দেওয়া হবে।

সেলাইন ইনজেকশন আরম্ভ হবার চার ঘন্টা পর আপনার/(আপনার রোগীর) থেকে আবার মল এবং অল্প পরিমান (১ml) রক্ত বিভিন্ন পরীক্ষার জন্যে নেওয়া হবে। এই চার ঘন্টায় কোন প্রস্রাব হলে সেটাও পরীক্ষার জন্য নেওয়া হবে।

সেলাইন ইনজেকশন আরম্ভ হবার আট ঘন্টা পর পরীক্ষার জন্য আবার প্রস্রাব ও মল নেওয়া হবে।

পরের দিন (সেলাইন ইনজেকশনের ২৪ ঘন্টা পর) শেষ বারের মত আপনার/(আপনার রোগীর) থেকে অল্প পরিমান রক্ত (১ml) প্রস্রাব এবং মল বিভিন্ন প্রকার পরীক্ষার জন্য নেওয়া হবে।

রোগ সেরে না যাওয়া পর্যন্ত আপনাকে/(আপনার রোগীকে) হাসপাতালে চিকিৎসাধীন রাখা হবে এবং চিকিৎসার উপযুক্ত ব্যবস্থা করা হবে। গবেষনা কালীন, রক্ত নেবার সময় সামান্য ব্যথা ছাড়া আপনার/(আপনার রোগীর) আর কোন প্রকারের শারীরীক অসুবিধা হবে না। আপনার সম্মতি আমাদেরকে এই "হাইপোগ্লাইসিমিয়া" রোগের উপযুক্ত চিকিৎসা বের করতে সাহায্য করবে।

অঃপৃঃ দ্রঃ

এই গবেষণায় অন্তর্ভুক্ত হওয়ার আরেকটি সুবিধা হচ্ছে যে আপনার/আপনার রোগীর রক্তে শূন্যতার পরিমাণ নির্ণয় করা হবে এবং তার যথাযথ চিকিৎসা করা হবে।

আপনি যে কোন সময় নিজেকে(আপনার রোগীকে)গবেষণা থেকে প্রত্যাহার করতে পারবেন। আপননি যদি এ গবেষণায় সম্মত নাও থাকেন তাহলেও আপনি/(আপনার রোগী) এ হাসপাতালের প্রচলিত সুচিকিৎসা পাবেন/(পাবে)।

আপনি ইচ্ছা করলে বিভিন্ন প্রকারের পরীক্ষার ফলাফল আপনাকে জানানো হবে। ধন্যবাদ।

গবেষকের স্বাক্ষর : _____

তারিখ : _____

স্বাক্ষীর স্বাক্ষর : _____

তারিখ : _____

রোগীর/অভিভাবকের স্বাক্ষর/
টিপসহি : _____

তারিখ : _____

Form # 1. DEXTROSE SOLUTION STUDY Budget No.: _____

HISTORY

Date & time: _____ I.V. soln.: _____ Study #: _____

Patient's name: _____ Adm. #: _____ Age: _____

PRESENTING COMPLAINTS:

DIARRHOEA:

a. Duration: _____ days.

b. Frequency in last 24 hours: 1 = 3-5 times, 2 = 6-10 times
3 = 11-15 times, 4 = 16-25 times,
5 = 16-25 times.

c. Character: 1 = Yellow liquid,
2 = Mucoid,
3 = Bloody mucoid.

VOMITING:

a. Duration: _____ days.

b. Frequency: 0 = No, 1 = 1-5, 2 = 6-10 (last 24 hrs)

ANOREXIA:

Duration: _____ days

0 = No, 1 = Yes

FEVER: 0 = No, 1 = Yes

ABDOMINAL PAIN: 0 = No, 1 = Central, 2 = Left side,
3 = Right side, 4 = Lower abdomen,
5 = Generalized.

LAST URINE PASSED: _____ hrs before admission

Urine volume: 0 = Normal, 1 = Scanty.

OUTSIDE MEDICATION: 0 = No
1 = Hemoeopathy
2 = Indegenous

COMMENTS: _____

Form #: _____ Budget #: _____

DEXTROSE SOLUTION STUDY

PHYSICAL EXAMINATION

Date & time: _____ I.V. soln: _____ Study #: _____

Patient's name. _____ Adm. #: _____ Age: _____

RADIAL PULSE: _____/ Rhythm: 0 = Regular, 1 = Irregular

Volume: 0 = Good, 1 = Low

RECTAL TEMP. _____/°F WEIGHT: (24 hrs post adm.) _____kg HEIGHT _____ cm.

WEIGHT FOR AGE: _____kg WEIGHT FOR HEIGHT(kg) _____

ARM CIRCUMF.(cm) _____

DEHYDRATION: 1 = Moderate
2 = Severe

ABDOMEN:

Distension: 0 = Absent
1 = Yes

Tenderness: 0 = Absent
1 = Left sided
2 = Right sided
3 = Generalised

Bowel sound: 0 = Normal
1 = Sluggish

Liver: 0 = Not palp
1 = Palp, non tender
2 = Palp tender

Form # 3

DEXTROSE SOLUTION STUDY

INVESTIGATIONS

Budget #: _____

Date & time: _____ I.V. soln: _____ Study #: _____

Patient's name: _____ Adm. #: _____ Age: _____

BLOOD CHEMISTRY:

Time	Na	K	Cl^-	HCO_3	Cr	Glc	Osm	Hct
0 hr								
4 hrs								
24 hrs								

URINE CHEMISTRY/STOOL VOLUME:

Time	U. vol (L)	(U)Glc.conc. (mmol/L)	Total glc(U) mmol	U.Osm	Stool volume (L)
0-4 hrs				4 hrs	0-4 hrs
4-8 hrs				8 hrs	4-8 hrs
24 hrs				24 hrs	0-24 hrs

STOOL CULTURES/INVESTIGATIONS:

Salmonellae

Shigellae

V. cholerae

ETEC ST/LT

Rotavirus Elisa

Total vol of I.V. soln. (l)	
Total duration of I.V. soln. (hrs)	
Total duration of hospital stay (days).	

STOOL MICROSCOPY:

pH

Puscells /hpf

RBC/hpf

Veg. Giardia

Veg. E.H.

Ova/Cyst.