Attachment 1. 8

Date 23.2.82

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. K. Zaman Trainee Investigator (if any) Nil

Application No 82-010(p) Dr. M. R. Islam Supporting Agency (if Non-ICDDR,B) _____

Title of Study Clinical presentation of hypokalaemia in children attending a rural diarrhoeal treatment centre in Bangladesh

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

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

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

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

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

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

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

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

Kzaman 23/2/82
Principal Investigator

Trainee

82-010(P)
Rec'd. 23.2.82

SECTION I - RESEARCH PROTOCOL

1. TITLE: Clinical presentation of hypokalaemia in children attending a rural diarrhoeal treatment centre in Bangladesh.

2. PRINCIPAL INVESTIGATORS: Dr. K. Zaman, Dr. M. R. Islam

   CO-INVESTIGATORS: Dr. A. H. Baqui, Dr. Emdadul Haque

3. STARTING DATE: March 15, 1982

4. COMPLETION DATE: June 15, 1982

5. TOTAL DIRECT COST: US $ 2989

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

Signature of Scientific Programme Head: Thomas Butler M.D.

Date: Feb 23 1982

This signature implies that the Scientific Programme Head takes responsibility for the planning, execution and budget for this particular protocol.

A-032003

7. ABSTRACT SUMMARY:

One of the most important health hazards to children in developing countries during diarrhoeal episodes is hypokalaemia. Not only can serious complications arise from this but also fatalities may occur particularly in malnourished children. Clinical presentation of hypokalaemia varies from case to case and is yet to be documerted. This study is proposed to find the prevalance and clinical features of hypokalaemia in 300 Bangladeshi children under 5 years of age during diarrhoea. After history taking a thorough clinical examination will be done by the Physician to note the sign symptoms and 2 cc of venous blood will be taken before initiating any treatment. Serum potassium and bicarbonate level will be measured along with other routine investigations of blood. At the same time an ECG will be done in all cases to find any abnormality. The child will get usual diarrhoeal treatment along with potassium supplementation per orally or intravenously as required. At the time of discharge another 2 cc of venous blood will be taken to compare with the initial findings.

8. REVIEWS:

a) Research involving human subject

b) Research Committee

c) Director

d) BMRC

e) Controller/Administrator

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

The objective of this study is to document the prevalance and clinical features of hypokalaemia observed in the patients under 5 years of age attending Matlab Diarrhoeal Treatment Centre.

2. Background

Matlab, the rural treatment centre of ICDDR,B is located in Comilla district about 45 km south-east of Dacca and treats diarrhoeal patients at an average of 10,000 - 12,000 per year of which 4000-6000 come from a well defined study area. The treatment centre is staffed by Physicians, para-professionals and other supporting staff. Diarrhoeal mortality is very low in uncomplicated cases and is significantly higher in cases with associated complications. There are many complications associated with diarrhoea of which hypokalaemia is one of the major problems. It was found that mortality is much greater in hypokalaemic patients than normokalaemic patients. [1,2]

Potassium is the major intracellular cation, only a small fraction (2 percent) of 2500 to 3000 meq of potassium within the body is contained in the extracellular space. [3,4,5] Disturbance of potassium equilibrium may produce a wide range of clinical disorders.

During diarrhoea along with other electrolytes potassium is losed in the stool. Molla et al [6] have studied the stool electrolyte contents of acute watery diarrhoeas of children under 5 years of age suffering from diarrhoea due to V. cholerae, ETEC & rotavirus. They observed that children looses more than 30 mmols potassium/L in these three types of diarrhoeas (cholera 30 ETEC-37 and rotavirus 38 mmols/L). Also the stool of child contain more potassium than the stool of adult in cholera. [7]

As far as potassium is concerned, the literature so far has demonstrated widely diverging opinions on the adequacy of the serum potassium concentration as a reliable guide to the diagnosis of potassium deficiency. [8] Radioisotope dilution studies have been performed by several investigators on patients with different diseases and on healthy human beings, as well as on animals of different kinds. The interpretations of results have been somewhat conflieting. Moore et al [9] have found no correlation between the serum potassium concentration and total exchangeable potassium. These findings were confirmed by Flear et al.[10] These two investigations expressed total exchangeable potassium on the basis of unit body weight. When Leibman and Edelman [11] referred their results to dry body solids, they found a significant correlation between the serum potassium concentration and total exchangeable potassium. Sterns et al [3] concluded that in state of potassium depletion, the change which occurs in the plasma potassium concentration is strongly influenced by associated changes in internal potassium balance.

In their classic review of the subject, Scribner and Burnell,[12] basing their conclusions primarily on metabolic balance studies performed by Schwartz and Relman,[13,14] estimated that a reduction in the plasma potassium concentration from 4 to 3 meq/L is associated with a 100 - 200 meq total potassium deficit and that a further reduction from 3 to 2 meq/L is associated with an additional 200 - 400 meq deficit.

Several investigators observed myopathy in hypokalaemia.[4,5,15] J. Wainwright et al[15] found that there was marked muscle wasting, diminished tone, power and reflexes in all limbs but sensation was intact in hypokalaemic patient. In hypokalaemic periodic paralysis, it was observed that the limb and limb girdles are predominantly affected, the lower extremities usually more than the upper and there may be respiratory or bulbar muscular weakness.[16] Hypokalaemic periodic paralysis also observed by Howes EL et al,[17] Ionasescu V et al.[18] Hypokalaemia may be a cause of death in a patient with advanced muscular Dystrophy.[19]

Association of Hypokalaemia & cardiac arythmia is well established. It has been extensively studied by different investigators and may be in the form of ventricular premature beat, Atrial tachycardia, Nodal tachycardia, Ventricular tachycardia, Ventricular fibrillation or mild atrioventricular or intraventricular conduction defects.[20,21,22,23,24]

Disturbance of renal function is observed commonly in patients with potassium depletion. It has been studied both in man and animals.[25, 26,27] Concentrating defect of the kidney probably due to elevated rates of intrarenal prostaglandin synthesis which antagonises the action of antidiuretic hormone.[28,29] Symptoms of nocturia, polydipsia are frequently encountered.

3. Rationale:

Diarrhoea is one of the major causes of morbidity and mortality of children in Bangladesh. Throughout the developing world 10 percent of children die from the effects of diarrhoea before reaching their fifth year.[31] Death is mainly due to lack of proper treatment and complications. So it is very important to establish the prevalance and clinical findings of hypokalaemia as a complication of paediatric diarrhoea particularly in malnourished children. Above all, this study will enable us to comment on the level of decrease in serum potassium which produces the sign symptoms and whether this is more common in malnourished than wellnourished children.

B. SPECIFIC AIMS:

1. To find out the prevalance of hypokalaemia in children below 5 years of age.

2. To document the sign symptoms of hypokalaemia.

3. To compare the prevalance of hypokalaemia in malnourished and wellnourished children.

4. To see any variation in sign symptoms of hypokalaemia in the two groups of children and to compare this with a control group.

5. To find out the level of decrease in serum potassium which produce the sign symptoms.

C. METHODS AND PROCEDURES:

1. Subjects: 300 patients all under five years of age living in the census area of Matlab will be included in the study. Patients will be selected each morning with the first 3 children fulfilling the above criteria.

   The parents of the children will be informed of the study and if they agree to participate will be included in the study.

2. Clinical Procedures: Selected patients will be examined very carefully by two Physician independantly and they will note the sign symptoms without consulting each other to look interphysician variability. Both the Physician will be unaware of the electrolyte result and the result will be submitted to a third person to avoid any biasness. A scoring system will be carried out for each finding. 2 cc of venous blood will be taken for estimation of serum potassium, sodium & bicarbonate level along with other investigations before initiating

any treatment. ECG will be done at the same time. Nutritional status of the patient will be calculated on the basis of age/weight and height/weight. Discharge weight will be taken as his/her expected weight. Urine analysis will be done as soon as possible for specific gravity, protein or cast. Urine frequency and volume will be measured in the first 24 hours after admission. Hypokalaemia will be considered as a serum potassium level lower than 4 mmol/L [30] and the extent of hypokalaemia will be regarded as <4 to 3 - mild, <3 to 2 - Moderate and <2 - Severe. [4] From these findings it will be possible to show the average points scored by each group of patients. Patients whose serum potassium level is above 4 mmol/L will be considered as the control group (cases of Hyperkalaemia, serum potassium $\geq$ 6.5 mmol/L will be excluded from the study). Scoring will also be done on this group. Lethargy will be considered severe when the child is unable to hold up his head in the sitting posture. Muscular weakness will be judged on muscle tone & power. Severity of cardiac arrythmia will be considered depending on pulse, heart on auscultation and on ECG. Acidosis will be severe when the bicarbonate level falls below 15 meq/L and will be considered mild to moderate when between 15 and 20 meq/L. Clinically it should be recognised by noting the rate & depth of respiration. Severe acidosis will be considered when the child takes respiration more than 30/m (in cases of no other complications). Nephropathy will be diagnosed by low urine specific gravity, presence of protein or cast in urine.[25] ECG findings will be judged on the basis of T wave depression, appearance of U wave, long ST segment, prolongation of QU as well as QT interval.[32] Patients will get usual diarrhoeal treatment and potassium will be supplemented orally or intravenously as and when necessary. Before discharge of patient 2 cc of venous blood will be taken for estimation of serum potassium, sodium and bicarbonate to compare with the initial findings.

SCORING SYSTEM

		2	1	0
1.	Lethargy	Severe	Slight	No
2.	Muscular Weakness	Severe	Slight	No
3.	Abdominal Distension	Hugely	Slight	No
4.	Bowel Sound	Absent	Faint	Normal
5.	Cardiac arrythmia	Severe	Little	No
6.	Acidosis	Severe	Mild to Moderate	Absent
7.	Nephropathy	Marked	Slight	No
8.	ECG finding	Great Variation	Slight	No

3. Analysis of Data

There will be a flow sheet for each patient. Dummy tables will be made from these and results will be set out as follows:

Table I

Distribution of children under five by potassium level.

Potassium level mmol/L	No.of children	Percentage
Mild (< 4 to 3)	.	.
Moderate (<3 to 2)	.	.
Severe (< 2)	.	.
Normal	.	.
Total	300	300

Table II

Distribution of children by Hypokalaemia and score.

Potassium level	Score		
	0-4	5-9	10-16
Mild	.	.	.
Moderate	.	.	.
Severe	.	.	.
Normal	.	.	.
Total	.	.	.

X^2 count to see the difference in distribution pattern.

Table III

Distribution of children by Hypokalaemia level and nutritional status.

Hypokalaemia level	No. of Children	
	Malnourished	Wellnourished
Mild (<4 to 3)	.	.
Moderate (<3 to 2)	.	.
Severe (<2)	.	.
Normal	.	.
Total		

Table IV

Distribution of children by Score, Hypokalaemia level & Nutritional status.

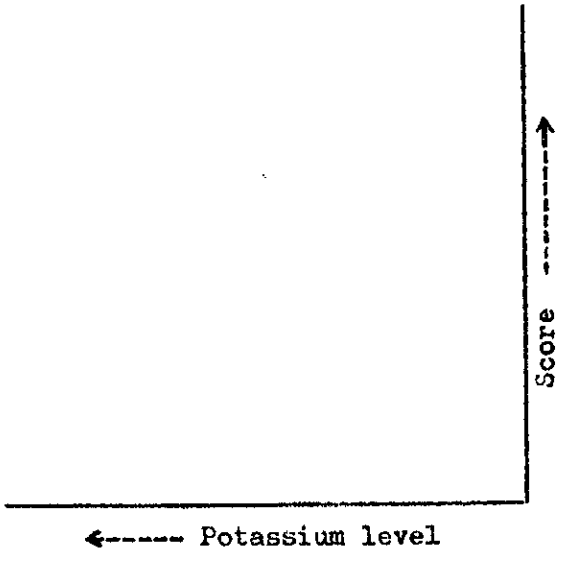
Hypokalaemia Level	Score					
	0 - 4		5 - 9		10 - 16	
	MLN	WLN	MLN	WLN	MLN	WLN
Mild	.	.	.	.	.	.
Moderate	.	.	.	.	.	.
Severe	.	.	.	.	.	.
Normal	.	.	.	.	.	.
Total						

MLN = Malnourished

WLN = Wellnourished

Table V

Graph according to score and potassium level.



D. SIGNIFICANCE

Results from this study will facilitate in therapeutic measures of paediatric diarrhoea in areas where there are no good laboratory facilities. This study may also define strategies for more efficient potassium concentration in fluids for treating diarrhoeas in children particularly in malnourished.

E. FACILITIES REQUIRED

1. No new office space is required.
2. Laboratory for routine biochemistry will be utilised.
3. No new lab. space is required.
4. No extra space in the treatment centre will be utilised.
5. Logistic support - none
6. Major items or equipment - no new items is required.
7. Other - none

F. COLLABORATIVE ARRANGEMENT

Nil

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2. Lawson DH et al : Severe hypokalaemia in hospitalised patients. Arch Intern Med. 139(9), 978-80, Sept.'79.

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28. Barry M. Brenner et al: Tubulointerstial diseases of the kidney. Harrisons principles of internal medicine 9th edition.

29. Robert W Schrier: Other specific renal diseases. Cecil Text Book of Medicine, Fifteenth edition.

30. Mutchisons Clinical Method - Fifteenth edition.

31. Population Reports from the Johns Hopkins University, series 1 No. 2 Nov.-Dec. 1980.

32. Robert Myerburg: Electrocardiography from Harrisons Principles of internal Medicine - 9th edition.

SECTION III - BUDGET

DETAILED BUDGET

1. Personal services.

Name	Position	% of effort	Project Tk.	Requirement Dollar
Dr. K. Zaman	Principal Investigator	20%	2300	
Dr. R. Islam	" "	5%	2600	
Dr. A. H. Baqui	Co-Investigator	10%	1200	
Dr. Emdadul Haque	"	10%	1100	
3 Staff Nurse		10%	1800	

2. Supplies & Materials

Electrolyte estimation 600 specimen @ 12 Tk.	7200
Urine examination 300 specimen @ 2 Tk.	600
ECG for 300 cases @ 5 Tk.	1500
Syringe, needle, paediatric urine collection (PUC) bag.	500

3.	Equipment ...	Nil
4.	Hospitalisation - 300x3 days x Tk.50 per day	45000
5.	Transport ...	Nil
6.	Travel ...	Nil
7.	Transport of things -	Nil
8.	Rent ...	Nil
9.	Printing: Forms & Publications	2000
10.	Contractual service -	Nil
11.	Construction ...	Nil

BUDGET SUMMARY	TAKA	DOLLAR
1. Personnel	9000	-
2. Supplies	9800	-
3. Equipments	-	-
4. Hospitalisation	45000	-
5. Transport	-	-
6. Travel	-	-
7. Transport of things	-	-
8. Rent	-	-
9. Printing	2000	-
10. Contractual service	-	-
11. Construction	-	-
Total	65800	-

Incremental Cost excluding personnel salary 56800

Conversion rate $ 1 = Tk. 19
= $ 2989

Grand Total = $ 2989

CONSENT FORM

One of the most important complication in children during diarrhoea is hypokalaemia, usually presents with muscular weakness, abdominal distension and cardiac involvement and the case may turn into fatality. We would like to document the prevalance and sign symptoms of hypokalaemia. We hope for the greater interest of mankind you will allow your child to participate in this study.

If you like to participate in our study your child may be needed to stay in the hospital at least 2/3 days or more until diarrhoea stops. For the purpose of study 2 blood samples (about 2 cc each time) will be taken from your child for serum electrolyte estimation while you are in the hospital.

If you don't like to participate in the study still your child will get best possible treatment.

You are at liberty to withdraw your child from the study at any time without any obligations and jeopardizing your medical care and treatment.

If you are voluntarily willing to participate in the study, then please sign your name or give left thumb impression below.

Signature of Investigator
Date _____

Signature or LTI of the legal guardian of the child
Date _____

সম্মতি পত্র

শিশুদের উদরাময়ের সময়ে যে সমস্ত জটিলতা দেখা যায় হাইপোকেলিমিয়া (পটাশিয়াম লবনের অভাব জনিত জটিলতা) তাদের মধ্যে অন্যতম। এতে শিশুর মাংসপেশী দুর্বল হয়ে যায়, পেট ফুলে যায়, হৃদযন্ত্রর ব্যাঘাত ঘটতে পারে, এমনকি শিশুর মৃত্যু পর্যন্ত হতে পারে। আমরা এই গবেষনায় হাইপোকেলিমিয়ার লক্ষনগুলি দেখতে চাই। আমরা আশা করি মানবতার বৃহত্তর স্বার্থে আপনি আপনার শিশুকে এই গবেষনায় অংশগ্রহন করতে দেবেন।

আপনি যদি গবেষনায় অংশগ্রহন করতে চান তাহলে আপনার শিশুকে ২/৩ দিন বা পায়খানা ভাল না হওয়া পর্যন্ত হাসপাতালে থাকতে হতে পারে। এই সময়ে আমরা গবেষনার প্রয়োজনে আপনার শিশুর নিকট থেকে পরীক্ষার জন্য দুবার রক্ত নেব (প্রতিবারে মাত্র দুই সি.সি)।

আপনি গবেষনায় অংশগ্রহন করতে না চাইলেও আপনার শিশুর চিকিৎসার কোন ত্রুটি হবে না।

গবেষনায় অংশগ্রহন করার পরও যে কোন সময়ে আপনি আপনার শিশুর নাম এই গবেষনা থেকে প্রত্যাহার করতে পারবেন।

আপনি যদি স্বেচ্ছায় গবেষনায় অংশগ্রহনে রাজী থাকেন তবে নীচে স্বাক্ষর করুন কিংবা বাম বুড়া আঙ্গুলের ছাপ দিন।

রোগীর অভিভাবকের
স্বাক্ষর / টিপসহি _____

তারিখ _____

_____
গবেষকের স্বাক্ষর

_____
তারিখ

HYPOKALAEMIA STUDY

Name_____ Hospital No._____ Date & Time of admission_____ Date & Time of discharge_____

Case No.	age	Sex	Dehydration status Mild/Mod./ Mod. Severe/ Severe	Weight (Discharge weight) (kg)	Height (cm)	Nutritional status Mal/Well nourished	ON ADMISSION			ON DISCHARGE		Urinary findings	Scoring in each item								Total score
							Serum level of K^+ (mmol/L)	Level of Hypokalaemia as categorised. Mild/Mod./ Severe/Normal	Blood Bicar-bonate level. (mmol/L)	Serum Potas-sium (mmol/L)	Blood Bicar-bonate (mmol/L)	volume frequency, specific gravity any protein or cast	1	2	3	4	5	6	7	8	