

ETHICAL REVIEW COMMITTEE, ICDDR,B Library

Form-12

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Principal Investigator DR SULTANA-KHANUM Trainee Investigator (if any) _____
 Application No. 84-012(P) KHANUM Supporting Agency (if Non-ICDDR,B) _____
 Title of Study Effect of Zinc and Copper Project status: _____
Implementation on the Dietary Intake and () New Study
of Weight-gain in Bangladeshi () Continuation with change
Children Recovering from Severe Malnutri- () No change (do not fill out rest of form)
tion.

Give 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

Risks 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

Risks 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

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 NA

d) Sensitive questions Yes No NA

e) Benefits to be derived Yes No NA

f) Right to refuse to participate or to withdraw from study Yes No

Confidential handling of data Yes No

Compensation &/or treatment where there are risks or privacy is involved in any particular procedure Yes No NA

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.

To obtain approval of the Ethical Review Committee for any changes affecting the rights and welfare of subjects before making such change.

Shanum
Principal Investigator

21 MAR 1984

Trainee

SECTION I - RESEARCH PROTOCOL

1. Title EFFECT OF ZINC AND COPPER SUPPLEMENTATION ON THE DIETARY INTAKE AND RATE OF WEIGHT-GAIN IN BANGLADESHI CHILDREN RECOVERING FROM SEVERE MALNUTRITION.
2. Principal Investigator: Sultana Khanum
- Co-investigator: A.N. Alam
Akbar Ali
Medical Officer (CNU)
- Consultant: M. Mujibur Rahaman
3. Starting Date April 15, 1984
5. Completion Date October 14, 1984
5. Total Direct Cost: US\$ 2917
6. Scientific Program Head:

This protocol has been approved by the Nutrition Working Group

Signature of Associate Director

M. Mujibur Rahaman

Date

28/3/1984

7. Abstract Summary:

Seventy five children aged between 6 months to 6 years admitted to the Children's Nutrition Unit (CNU), Dhaka with severe degree of Protein Energy Malnutrition (PEM) will be selected for the study. Zinc and copper supplementation will be given to two study comprising groups 25 in each group. One will receive zinc alone and the second group copper alone in addition to CNU diet and other supplementation. A third control group of 25 children will be offered usual CNU diet and other supplements as given routinely to other patients. The effect of zinc and copper on the dietary intake and rate of weight gain in Bangladeshi children recovering from severe malnutrition will be studied.

8. Reviews:

- (a) Research Involving Ethical Review Committee: _____
- (b) Research Review Committee: _____
- (c) Director: _____

SECTION II - RESEARCH PLAN

INTRODUCTION:

1. Objective

- a. To study the effect of zinc and copper supplementation in malnourished children during nutritional rehabilitation on dietary intake.
- b. To study the rate of weight gain in zinc and copper supplemented and nonsupplemented PEM children during recovery.

2. Background:

Zinc is needed for tissue synthesis both as a component of new tissue and in the forms of zinc metallo-enzymes essential for nucleic acid, protein and hormone (i.e. insulin) synthesis. Studies indicate that the size of body zinc store is extremely limited so that there is a day-to-day requirement for dietary zinc^(1,2). In normal children zinc is required to support growth as well as to replace losses. Hambidge's group has shown that a diet marginal in zinc may be the cause of failure to thrive in North America^(3,4). Zinc and vitamin A are linked through the enzyme retinol alcohol dehydrogenase, essential for the oxidation of retinaldehyde, the vitamin A aldehyde and also through the need for zinc in synthesis of retinol binding protein. The continual formation of the visual pigment is of utmost importance in the prevention of night blindness⁽⁵⁾. Children recovering from PEM may gain weight at over 20 times the normal rate. In this situation where the requirements for new tissue synthesis dominate the total dietary requirements the amount of zinc that has to be utilized by the new tissue may exceed the dietary supply. When this is the case only zinc may both limit the absolute rate of weight gain and determine the composition of new tissue laid down⁽⁶⁾.

Serum zinc and copper level were estimated in 130 severely malnourished children admitted to CNU, Dhaka on admission and during recovery (3-6 weeks) ⁽⁶⁾. The serum zinc and copper levels were found to be significantly low in all 3 types of PEM (marasmus, kwashiorkor and marasmic-kwashiorkor) compared to 50 age matched healthy controls. After nutritional rehabilitation the serum level of zinc and copper increased in all 3 types but did not reach the normal level (80-14 ug/dl). However, retinal Binding protein and albumin levels were not estimated due to non-availability of laboratory back up. Golden and Golden ⁽⁷⁾ found that there was an immediate and definite increase in their rate of weight gain with zinc supplementation in 14 of 16 PEM cases. /6

Until recently the concept of copper deficiency in man was not widely accepted. Copper deficiency developed in severely malnourished children rehabilitated on milk-based low copper diet was reported by Cordavo Basert and Graham in 1964 ⁽⁸⁾. In another study they diagnosed copper deficiency in premature and malnourished infants in 1969. Copper deficiency was then observed in untreated malnourished infants by Holtzman et al in 1970 ⁽⁹⁾. Keppel and Peden in 1972 observed copper deficiency in malnourished infants alimented exclusively on intravenous route ¹⁰. Goel, Misra and Seth in 1980 found a reduced plasma copper level in all types of PEM with the mean levels being same in marasmus and marasmic-kwashiorkor ¹¹. Khalil et al in 1974 found significantly lower plasma erythrocyte copper in PEM cases than in normal controls ¹². Duran et al reported decreased copper level on admission and during recovery stage of nutritional marasmus ¹³.

An analysis of 2136 hospital cases records of PEM cases from CNU showed that inspite of higher energy intake (200 kcal/day) during recovery (2-4 weeks) the rate of growth was not satisfactory. There was no correlation between higher energy intake and rate of weight gain. In these cases zinc or copper or both might have been limiting factors.

3. Rationale:

If the study is done successfully the rate of weight gain will be expected to be faster, patients will achieve maximum catch up growth in a shorter rehabilitation time, resulting in rapid hospital bed turn over. This way treatment cost per patient will be reduced. More over if discharged with a better nutritional status the long term effect of rehabilitation will be very satisfactory in terms of morbidity and mortality.

METHODS OF PROCEDURE:

- 1) Seventy five malnourished children between 6 months to 6 years of age who are recovering from malnutrition in the Children's Nutrition Unit will be selected for this study.
- 2) Children who are on antibiotics and having surgical injury, renal failure, tuberculosis, juvenile diabetes, liver diseases or patients resuscitated with heavy fluid or transfusion will be excluded from the study.
- 3) Their nutritional status will be determined by weight for height percentage of Harvard Standard and presence or absence of oedema. They will be divided into three groups with age matched controls. One group (controls) will get usual CNU diet and other supplements like rice, meat, vegetables, dal, milk (Table 1), folic acid, riboflavin, ascorbic acid, folfetab and high potency vitamin A capsules both as treatment and prophylaxies. In addition to CNU dietary regime one other group will get zinc alone and the third group will receive only copper supplements. Zinc is variably absorbed, moreover in Bangladeshi children there is considerable loss of zinc in various ways such as, perspiration, chronic diarrhoea etc. so zinc will be given at a dose of 5-10 mg/kg/day as sulphate. Copper supplement 80 mg/kg/day as copper sulphate will be given.

For the zinc and copper group the two elements will be given separately at separate times.

- 4) In these malnourished children, on admission to CNU, about 3 mls. of venous blood is drawn by jugular venepuncture for routined investigation like blood culture, TCDC, packed cell volume, haemoglobin, plasma protein, blood grouping etc. Three samples of 1 ml of blood will be needed for zinc, copper ceruloplasmin, RBP, prealbumin and serum transferin estimations for the study, that is on admission, and on weekly intervals. This collection will be made from our routine specimen. A further 1 ml blood sample (between 6 weeks to 6 months) after discharge may be needed.
- 5) Zinc and copper supplementation will be given from the third week after initial resuscitation period when weight gain is steadily increasing.
- 6) Stool and urine will be collected at intervals like that of blood.
- 7) Zinc and copper will be estimated from the food mixes used in CNU.

REFERENCES

1. Wilkins P.J., Grem P.C and Dreosti I.C. Plasma zinc as an indicator of zinc status in rats. Br. J. Nutr. 27: 113-120, 1972.
2. Hurley L.S., Swenerton H. Lack mobilization of bone and liver zinc under teratogenic conditions of zinc deficiency. J. Nutr. 101: 597-603, 1971.
3. Hambidge K.M., Hambidge C., Jacobs M and Baum J.D. Low levels of zinc in hair anorexia, poor growth and hypogeusia in children.
4. Walravens P.A., Hambidge K.M. Growth of infants fed on a zinc supplemented formula, Am. J. Clin. Nutr. 29: 1114-1121, 1976.
5. Kay R.C., Tasman, Jones C and Pybus J. Zinc and copper in human nutrition, J. Human Nutr, 35: 25-36, 1981.
6. Hussain S. Studies on serum zinc and serum copper levels in children of different nutritional status in Bangladesh. A thesis submitted for Master of Philosophy, University of Dhaka, 1983.
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8. Cordano A, Baertl J.M. and Graham G.G. Copper deficiency in infancy, paediatric, 34: 324-336, 1964.
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10. Keppel J.T. and Peden U.H. Copper deficiency in long term parenteral nutrition, J. Paed. 80: 32-36, 1972.
11. Goel R., Misra P.K. and Seth T.D. Study of plasma copper in protein energy malnutrition. Indian Paediatrics 17 (Nov) 869-873, 1980.

12. Khalil M., Kabil A., El-Khateeb S., Aref K., El-Lozy M, Jahin S. and Naseg F. Plasma red cells water and elements in PCM, Am. J. Clin. Nutr. 27 (March): 260-267, 1974.
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14. Khanum S. Protein energy malnutrition in urban Bangladesh. A dissertation for M. Sc. in community Health in developing countries London University: 1983.

Abstract Summary for Ethical Review Committee:

- 1) This limited study aims at achieving a rapid weight gain during rehabilitation of malnourished children in Bangladesh by giving zinc and copper supplementation. Rehabilitation of malnourished children is an expensive and long-protracted undertaking. As recovery is delayed due to some limiting factors, many hospital beds are occupied for a long period and many children who need admission from the outpatient department are deprived of inpatient care due to very limited hospital beds. In this study, therefore, zinc and copper will be supplemented to hasten recovery (in the form of sulphates) at a safe and effective recommended dose along with usual treatment schedule offered at CNU to severely malnourished children aged between 6 months - 6 years during nutritional rehabilitation.
- 2) There are no potential risk involved.
- 3) The patients will be under consistent observation of physicians and nurses and will get optimum care necessary although there are no potential risk involve.
- 4) During data analysis only case number will be used.
- 5) Informed consent in a consent form will be obtained from the authorised legal guardian or the parents of the patient before being included in the study.
- 6) A brief interview is usually taken before admission to obtain clinical history of the disease.
- 7) The patient will get free treatment and care during study period and if successful will make early recovery.
- 8) Hospital record will required.

- 9) Follow up will be necessary upto 6 months after discharge which will not be a problem because follow-up is usually a part of our normal work.
- 10) One ml of blood on four occasions will be needed during the whole study period.

SECTION III - BUDGET

Personnel Services

1. Name	Position	% Effort	Project Requirement US\$
Dr. Sultana Khanum	Principal Investigator	30	-
Dr. A.N. Alam	Co-Investigator	5	200
Mr. Akbar Ali	"	5	150
Physician from CNU (to be named)	"	10	-
Dr. M.M. Rahaman	Consultant	-	-
Research Officer (Biochemistry)		10	200
2. <u>Supplies & Materials</u>			
Routine investigations including blood culture (to be done at the CNU) costing of biochemical assays (attached)			2367
3. Equipments		Nil	
4. Patient hospitalization		Nil	
5. Outpatient care		Nil	
6. ICDDR,B transport		Nil	
7. Travel			
8. Transportation of things and patients		Nil	
9. Rent, Communication, Utilities		Nil	
10. Printing & Publication		Nil	
11. Other contractual services		Nil	
12. Construction		Nil	
		Total	US\$ 2917

COSTING OF THE ASSAYS OF 75 SAMPLES

<u>Sl</u> <u>No.</u>	<u>Assay</u>	<u>No. of Samples</u>	<u>Rate in \$</u>	<u>Total Cost \$</u>
1.	Zinc	75	2.74	205.50
2.	Copper	75	2.74	205.50
3.	Pre-albumin	75	8.69	651.75
4.	Retinol binding protein	75	8.69	651.75
5.	Ceruloplasmin	75	8.69	651.75
		Total		\$ 2366.25

আনুষ্ঠানিক উদরাময় গবেষণা কেন্দ্র

স্মৃতি পত্র

আনুষ্ঠানিক উদরাময় গবেষণা কেন্দ্র এবং সি, এন, ইউ, পুষ্টিহীনতার উন্নত চিকিৎসা উদ্ভাবনের জন্য যৌথভাবে কাজ করে যাচ্ছে। পুষ্টিহীনতার চিকিৎসার বিভিন্ন সমস্যা আছে। তার মধ্যে একটা হচ্ছে পুষ্টি পুনর্বাসনের সময় ধীরে ওজন বাড়া। দ্রুত ওজন বাড়ানোর জন্যে সহযোগী উপাদান হিসাবে জটিক ও কপালের ব্যাপারে সম্যক ধারণা থাকা দরকার কেননা ইহা দ্রুত আরোগ্য ও ভাল ব্যাপস্থাপনায় সাহায্য করে। আমরা আপনার শিশুকে এই গবেষণায় অনুর্ত্তন করতে চাই।

- ১। আপনার শিশু উপযুক্ত চিকিৎসা পাবে।
- ২। মাত্র ১ সি সি করে মোট ৪ বার রক্ত নেওয়া হবে জৈব-রাসায়নিক পরীক্ষা করার জন্য।
- ৩। প্রয়োজনীয় সুস্পষ্ট খাবার ও ঔষধ সরবরাহ করা হবে।
- ৪। আপনার শিশু হয় জিক (৫-১০ মিঃ গ্রাঃ/কেজি/দিন) অথবা কপার (৮০ মিঃ গ্রাঃ/কেজি/দিন) ৩য় সপ্তাহ থেকে গ্রহণ করবে।
- ৫। অন্যান্য প্রয়োজনীয় পরীক্ষা নিরীক্ষা করা হবে।
- ৬। আপনার শিশু সম্পূর্ণ সুস্থ হওয়ার পর ছুটি দেওয়া হবে।
- ৭। আপনি যে কোন সময় গবেষণা থেকে শিশুকে প্রত্যাহার করে নিতে পারবেন। আপনার শিশু একই চিকিৎসা পাবে যদিও আপনি স্বেচ্ছায় এই গবেষণায় অংশ গ্রহণ না করান।

যদি আপনি এই গবেষণায় আপনার শিশুকে অংশগ্রহণ করতে ইচ্ছা করেন তবে দয়া করে নিম্নে স্বাক্ষর করুন বা বাম হাতের বুড়ো আঙুলের ছাপ দিন।

পরীক্ষকের স্বাক্ষর

বাম হাতের বুড়ো আঙুলের ছাপ

তারিখ-----

রোগীর সাথে সম্পর্ক