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REVIEW BOARD ON THE USE OF HUMAN VOLUNTEERS

CRL

Principal Investigator Dr. R. Islam Trainee Investigator(if any) _____

Application No. 78-023 Supporting Agency(if Non-CRL) _____

Study: Comparison of Labon-Gur (common salt+brown sugar) with labon-Gur-Soda (common salt+brown sugar+ dibicarb) as oral rehydration solution in Diarrhea.

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):

Types of Population:
Ill subjects — Yes / No
Non-Ill subjects — Yes / No
Minors or persons under guardianship — Yes / No

Does the study involve:
Physical risks to the subjects — Yes / No
Social risks — Yes / No
Psychological risks to subjects — Yes / No
Discomfort to subjects — Yes / No
Invasion of privacy — Yes / No
Disclosure of information possibly damaging to subject or others — Yes / No

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

Subjects clearly informed about:
Nature and purposes of study — Yes / No
Procedures to be followed including alternatives used — Yes / No
Physical risks — Yes / No
Sensitive questions — Yes / No
Benefits to be derived — Yes / No
Right to refuse to participate or to withdraw from study — Yes / No
Confidential handling of data — Yes / No

5. Will signed consent form be required:
Adult subjects — Yes / No
From parent or guardian if subjects are minors — Yes / No
What actions be taken to protect subjects: — Yes / No

The following being submitted herewith.

✓ Copy of proposal - Initially submit abstract only (all other requirements will be submitted with individual studies).
✓ Questionnaire (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. Information as to when the questionnaire will be presented to the Board for review.

It is necessary to obtain approval of the Review Board on Use of Human Volunteers for any changes involving the rights and welfare of subjects before making such change.

K. Islam
Principal Investigator

Trainee

Recd 11/9/78

78-023

SECTION 1 - RESEARCH PROTOCOL

1) Title: Comparison of Labon-Gur (common salt+brown sugar) with Labon-Gur Soda (common salt+brown sugar+ sodibicarb) as Oral Rehydration solution in Diarrhea.

2) Principal Investigator: Dr. R. Islam

3) Starting Date: 1st October 1978

4) Completion Date: 31st October 1978

5) Total Direct Cost: $ 5772

6) Abstract Summary: (250 words or less)

A double blind comparative clinical trial to observe the effectiveness of oral solutions containing only common salt and brown sugar with and without added bicarbonate, is planned on diarrhea patients with any degree of dehydration. Approximately 100 patients will be studied. Failure will be considered when the solution fail to correct initial dehydration, maintain hydration or electrolyte imbalance at any time of study and these patients will be treated with indicated standard intravenous and/or oral replacement solutions.

7) Review:

a) Research Involving Human Subjects : _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION 11 - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

The main objective of this study is to find out an effective but cheap solution with ingredients that are readily available at the remotest corner of developing countries so as to reduce morbidity and mortality resulting from diarrheal diseases of any etiology.

2. Background: Diarrheal disease is the leading and probably most important cause of morbidity in the developing world and hydration remains the most important aspect of treatment of diarrheal diseases. Primary therapy is, therefore, to correct initial dehydration and subsequently maintaining hydration. Previously this could be accomplished only with intravenous fluid alone but now it is possible to manage most episodes of diarrheal diseases effectively with oral therapy alone. Now is it beyond doubt from controlled studies that there is very little difference in the effectiveness of glucose-electrolyte and sucrose electrolyte solutions. It was observed from several studies that patients admitted with acute onset of diarrhea has CO_2 levels of about 14-16 mEq/L and K-5 mEq/L on admission and as such are not severely acidotic and hypokalaemic. We have observed few patients developed carpopedal spasms, particularly in lactating mothers, due to alkalosis when they are hydrated with standard WHO recommended oral solutions containing bicarbonate. It has been proven that no gross damage of the mucosal is present in most of the watery diarrheas due to V.cholerae, E.coli, rotavirus etc. Glucose facilitates the absorption of sodium. With adequate kidney functions, electrolyte imbalances are gradually corrected. And gradual correction of electrolyte is clinically desirable than rapid correction.

The efficacy of oral fluid is well established and we are facing only with the problem of apparent failure due to non-availability of ingredients when it was transferred from an institution to a village setting. Recent studies by me of Labon-gur (common salt+brown sugar) as oral rehydration solution in the treatment of diarrheal disease in adults has shown that it can effectively replace WHO formulation of sucrose-salt

electrolyte solution for adults with moderate dehydration when started at its early stage.

The condition of that study were designed to match these in ordinary therapeutic circumstances without specialised equipment and personnel. It was observed that some patient remained acidotic even after 24 hours of therapy although they are clinically not looked acidotic.

3. Rationale: At the presentmoment, it is very important and necessary to determine the adequacy and limitations of Labon-gur by comparing in a double blind way to labon-gur-soda solutions in all age group.

B. SPECIFIC AIMS:

Compare the effectiveness of simple labon-gur —— with labon-gur-soda solution in the correction of dehydration and electrolyte imbalance due to watery diarrhea of any etiology with ultimate aim to propagate this simple treatment in rural Bangladesh.

C. METHODS OF PROCEDURE:

1. Patients Population: A sample of patients from different age group (6 months to 60 years) with moderate to severe dehydration due to acute diarrheal episode of short duration who have not received any antibiotics during the last week and who have given informed consent, will be admitted for study. The first 4 patients each day with the above criteria will be taken for study until 100 patients have been studied, 50 in each group.

2. Clinical Informations: Every patient will receive standardize physical examination including vital sign, admission weight, degree of clinical dehydration etc. Blood will be drawn for electrolyte, blood sugar, creatinic, specific gravity and all acute sera for antibody determination. A catheter stool specimen will be obtained for culture, microscopic examination and also for rotavirus antigen.

3. Treatment of Patients: Each patient will be stratified as to the clinical degree of dehydration (mild, moderate and severe) and randomised in a double blind manner to one of two treatment groups.

Group 1 (Lobon-Gur solution) — will be treated as follows:

Severely dehydrated patient will be treated with standard intravenous solution (100ml/kg) as rapidly as possible. I.V. will then be removed and oral fluid will be used for subsequent maintenance. Mild and moderate dehydration will be dealt with only oral solution alone. Initial hydration will be tried over a 4-6 hours period (50-70 ml/kg).

Group 11 (Labon-Gur-Soda) — will be treated exactly as group 1, except that sodicarb will be added in this group.

Comparison of Fuilds:

Labon-Gur Solution	Labon-Gur-Soda
Na+ --87.0 m mol/L	Na+ --- 90 m mol/L
CL- --87.0 m mol/L	CL- --- 60 m mol/L
Brown sugar -111. 0 m mol/L which is made by	HCO_3^--- 30 m mol/L
Na --5 gm/L (approx. 1 teaspoonful)	Brown sugar --111 m mol/L which is made by
Brown sugar - 50 gm/L (approx. 10 teaspoonful)	Nacl -- 3.5 gm/L
	$NaHCO_3$—2.5 gm/L
	Brown sugar 50 gm/L

Maintenance: Replacement therapy will be continued until diarrhea stops which is — defined as a 24 hours period during which no watery stool has been passed. There will be no restriction of food and children will be allowed breast-feeding. Antibiotics will not be used unless specifically indicated (tetracycline will be used for cholera).

Intake and output records will be maintained 4 hourly for initial 4 hours and through every 8 hourly using cholera cots until diarrhea stops.

All oral intake will consist of the oral solution

until the feeding started at which time water will be available ad lib. To avoid vomiting, small amounts as sips will be given frequently. Patient will be discharged about 24 hours after diarrhea stops.

The need to resume intravenous fluids will be judged as a failure for the oral solution. Decision to resume intravenous fluids will be based on objective criteria.

i) A return of clinical signs of dehydration including loss of body weight.

ii) Persistent vomiting preventing the use of oral fluid.

iii) An increase in plasma specific gravity (>1.030)

If patients are restarted on intravenous fluids, after hydration, they again will be tried on the same solution received primarily. Failure due to electrolyte imbalance during therapy (Na <125, >150, K <2.5, > 6.0 and CO_2 <10, >30 mmol/L) will be treated with an appropriate solution intravenously and will be considered as a treatment failure.

Special Lab Tests:

Microbiology — E.coli from the stool culture will be tested for heat-labile enterotoxin using adrenal cell assay (or elisa assay) and for heat stable toxin using infant mice assay.

After the study is completed, it should be possible to compare Labon-gur with Labon-gur-soda groups as follows:

1. Admission values: Objective evidences of both the groups should be same. Also the pathogens isolated should be same.

2. Failure to hydrate or maintain hydration or to correct electrolyte imbalances.

3. Duration of diarrhea.

4. Volume of diarrheal stool.

5. Amount of fluid given both I.V. and Oral.

6. Any complications during therapy.

7. Acceptance of oral fluid.

Randomization to either Labon-gur or Labon-gur-soda will be done in a double blind manner. Mr. Akbar Ali, Biochemistry Branch, will prepare the two solutions and mark one solution "A" and the other "B". The code for "A" and "B" will be changed randomly. Prospective stratification of patients will be by the severity of the illness including degree of dehydration. But stratification by etiological agents will be by retrospective analysis. The data will be transferred to IBM cards for data storage and analysis.

D. SIGNIFICANCE:

From the result of this study, it should be possible to compare the safety and efficacy of Labon-gur over Labon-gur-soda solution in the treatment of watery diarrheal syndromes, throughout the whole world especially in rural areas of developing countries, like Bangladesh, whose medical facilities are very much limited.

Simple L-G solution formulation is about 6.67 times cheaper than more complex WHO formulation containing glucose-electrolyte.

E. FACILITIES REQUIRED:

1. Office for investigator in study ward already provided.

2. Laboratory facilities for routine bacteriology, biochemistry, clinical pathology will be utilized.

3. Hospital resources — the study ward will be utilized. Maximum of 5 patie s will be taken per day and on average 4 patients are needed per day. Thus a total of 12 beds will be sufficient. Study physicians will be needed to be present on the ward 24 hours per day to monitor therapy. A study nurse will be necessary round the clock during the study period.

4. Animal resources — E.coli from approximately 200 specimens will be tested for heat-stable toxin which will require approximately 400 infant mice.

5. Logistic support — 2 hours of computer time is anticipated.

6. Other specialised requirements - The two oral solutions will be prepared by the biochemistry branch without any knowledge of the investigators.

F. COLLABORATIVE ARRANGEMENTS: None

REFERENCES

1. Kielmana and McCord. Home treatment of child-hood diarrhoea in Punjab village; "Environmental child Health" August 1977.

2. Nalin, D.R. etal. "Sucrose in oral therapy for cholera and related diarrheoas". Lancet, June 28, 1975.

3. Suprapto, Soenarto, Bachtin etal. Oral sucrose therapy for diarrhoea. Lancet 2: 323(1975).

4. Palmer, D.L. etal. Comparison of sucrose and glucose in the oral electrolyte therapy of cholera and other severe diarrhoea. New. Eng. J. Med. 297:1107-1100(1977)

5. Sack, D.A. etal. Oral hydration in rotavirus diarrhea: A double blind comparison of sucrose with glucose electrolyte solution. (in publication).

6. Islam, R. Labon-Gur Study

7. Lancet. August 5, 1978

ABSTRACT SUMMARY

Comparison of Labon-gur with Labon-gur-soda as oral rehydration solution in diarrhoea.

1. Approximately 100 patients of all age group with any degree of dehydration due to uncomplicated diarrhoea will be admitted in the study ward.

2. Risk of this study are very small. Failure to rehydrate or to correct electrolyte imbalance are possible complications resulting from diarrhoea. To avoid these complications, patients will be closely followed round the clock by qualified nurses and physicians. Venepuncture blood samples will be required daily. This is a discomfort but not a significant risk.

3. Study physicians and nursing staff will be present in the ward 24 hours daily during the study to detect any treatment failures at an early stage and appropriate actions will be taken immediately.

4. Patients will be identified by CRL registration numbers. All records will be kept in a locked office. At the end of the study, identifying informations will be removed from study data sheets.

5. Signed informed consent will be taken from the patients or his/her legal guardian if the patient is a minor. The object and procedure of the study will be explained to the patients in Bengali and concerning patients will either sign or give thumb print in the consent form.

6. The study does not involve any interview.

7. The patient will be benefited by the treatment. Society, expecially rural Bangladesh and other developing countries will be benefited by determining the efficacy of this very cheap and easily available ingredients for the use in oral solutions in the treatment of diarrhoeal disease.

8. Data will be collected from the patient's hospital record. Only blood will be collected from the patient for study purposes.

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name	Position	%effort No. days	Annual salary	Taka	Dollar
Dr. R. Islam	Principal Investigator	50%	Tk.52,666	2195	---
2 study Physicians	Co-investi-tor	100%	Tk.27,084	4514	---
Technicians		50%	Tk.20,484	854	
8 study nurses		50%	TK.16,284	5428	----
Mr. Akbar Ali	Head, biochem.	10%	TK.32,076	267	---
Key Punch Clerk		5 days @ Tk.32/day		160	---
				13418	

2. SUPPLIES AND MATERIALS

Office supplies	Unit cost	Amount req.	Taka	Dollar
Office supplies misc.			1,000	
IBM Cards	$ 8	10,000	---	8
Computer Tapes	$ 8.19	1		8
Plastic glass wares				1000
Needles 21 g.	$ 0.05	500		25
Infant mice	Tk. 3/-	400	1,200	--
1½ ml vials, polypro-lene		500		25
Nutrient agar 1 lb.	$10.00	1		10
Computer time	Tk.650/-	2	1,300	--
			3,500	1076

3. EQUIPMENT : No new equipment needed.

4. HOSPITALISATION:

Number of patient days @ Tk.150.00	Tk.45,000
Routine tests (see attachment No.1)	Tk. 3,325

5. OUTPATIENT CARE: follow up - None

6. CRL TRANSPORT: None

7. TRAVEL AND TRANSPORTATION OF PERSONS: None

8. TRANSPORTATION OF THINGS: None

9. RENT /COMMUNICATION & UTILITIES. None

10. PRINTING AND REPRODUCTION:

Stencils	1000 pages	Tk. 200	
Publications			$300
Xerox		Tk. 500	

11. OTHER CONTRACTUAL SERVICES: - None

12. CONSTRUCTION, RENOVATION, ALTERATIONS: None

ATTACHMENT TO BUDGET No. 1

Routine Tests

	Biochemistry lab.	No. of test req.	Cost/test Tk.	total cost/TK.
Serum	Na^+	500	0.50	Tk.250
Serum	K^+	500	0.50	Tk.250
Serum	CL^-	500	0.25	TK.125
Serum	CO_2^-	500	1.00	TK.500
Serum	Glucose	100	1.00	TK.100
Serum	Creatinin	100	1.00	TK.100
Serum	Sp. Gravity	500	0.25	TK.125
		TOTAL BIOCHEMISTRY:		TK. 1450/-

Bacteriology

Culture of stool	100	15.50	Tk.1550

Clinical Pathology

Dark field	100	1.00	Tk.100
Stool microscopy	100	2.00	TK.200
F.Blood Sp.gravity	100	0.25	TK.25
			TK.325
		TOTAL ROUTINE TESTS:	TK. 3325.00

B. BUDGET SUMMARY

Category		Taka	Dollar
1.	Personnel	13,418	---
2.	Supplies	3,500	1076
3.	Equipment	---	---
4.	Hospitalisation	48,325	---
5.	Outpatients	---	---
6.	CRI. Transport	---	---
7.	Travel Persons	---	--
8.	Transportation of things	---	---
9.	Rent/Communication	----	---
10.	Printing/Reproduction	700	300
11.	Contractual Service	--- -	---
12.	Construction	---	---
	TOTAL:	65,943	1376

TOTAL : $ 5772

Conversion rate $1.00 = Taka 15.00

CONSENT FORM

Comparison of Labon-Gur with Labon-Gur-Soda as Oral Rehydration Solution in Diarrhoea

The Cholera Research Laboratory is carrying out research to determine the most economic and effective way to treat diarrhoea. We like you to participate in this study. This is found quite safe and effective in correcting dehydration due to diarrhoea in CRL and other places also. If you decide to participate in the study, you can expect that :

1. You will be treated for diarrhoea.
2. You will be needed to stay in the hospital until your diarrhoea stops.
3. While you are in hospital, you will need to have blood tests done every day. These are all routine tests and no special or hazardous test will be done.
4. If the present oral solutions fail to treat you, we will give you intravenous solutions or other oral solutions.
5. If you do not like to participate in the study, you will be treated like ohters in this hospital without any obligations.
6. If you wish, you can withdraw yourself from the study at any time without jeopardizing your medical care and treatment.

Realising and understanding fully if you agree to participate voluntarily in this study, please sign your name below.

_____

Signature or thumb impression of the patient or child's legal guardian.

Date; _____

_____

Signature of Investigator

CRL Case No.: _____

কলেরা রিসার্চ ল্যাবরেটরী ঢাকা

সম্মতি পত্র

প্রাপ্ত বয়স্কদের উদরাময় রোগে লবণ ও গ্লুকোজ মুখে খাওয়ার স্যালাইন দিয়ে চিকিৎসা

এই কলেরা হাসপাতালে সব চেষ্টাই করা হচ্ছে, যাতে আপনি এবং উত্তরকালে কিভাবে উদরাময়ের চিকিৎসা করা যায় সে জন্য গবেষণা চালিয়ে যাচ্ছি। আমরা উপরোল্লিখিত পদ্ধতিতে আপনার উদরাময়ের চিকিৎসা করতে চাই। অন্য কয়েকটি স্থানে এই পদ্ধতির কার্যকারিতা প্রমাণিত হয়েছে। আপনি এতে অংশ গ্রহণ করতে চাইলে নিম্নলিখিত নিয়মাবলী মেনে চলতে হবে।

১। আপনার উদরাময় রোগের যথাযথ চিকিৎসা করা হবে।

২। পাতলা পায়খানা বন্ধ না হওয়া পর্যন্ত আপনাকে হাসপাতালে থাকতে হবে।

৩। এখানে থাকাকালীন রোজ আপনার রক্তের প্রাথমিক পরীক্ষা করা হবে এবং এতে আপনার কোন ক্ষতি হবে না।

৪। যদি এই মুখে খাওয়ার স্যালাইনে আপনার রোগ ভাল না হয় তাহলে অন্য রকম স্যালাইন বা শিরায় স্যালাইন দেয়া হবে।

৫। এই পদ্ধতিতে চিকিৎসায় রাজী না হলেও এ হাসপাতালে আপনার সঠিক চিকিৎসার অভাব হবে না।

৬। যে কোন সময়ে আপনি এই পরীক্ষামূলক চিকিৎসা থেকে আপনাকে সরিয়ে নিতে পারেন এবং তাতে আপনার প্রচলিত চিকিৎসার কোন ক্ষতি হবে না।

যদি স্বেচ্ছায় এই পরীক্ষামূলক চিকিৎসায় রাজী থাকেন এর নীচে স্বাক্ষর করুন।

সাক্ষীর স্বাক্ষর

রোগীর স্বাক্ষর বা টিপসই

তারিখ ________

হাসপাতাল নম্বর ________