Attachment 1.

Date 12.12.79

REVIEW BOARD ON THE USE OF HUMAN SUBJECTS, ICDDR,B.

Principal Investigator Dr. R. Islam

Application No. 80-003

Title of Study Gram-negative shock : effect of Corticosteroids

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

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

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

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes (No)
   (c) Minors or persons under guardianship (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects (Yes) No
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) (Yes) No
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions Yes (No)
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure Yes (No)
5. Will signed consent form be required:
   (a) From subjects (Yes) No
   (b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Board:
   ___ 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 fot 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 Board for review.

We agree to obtain approval of the Review Board on the Use of Human Subjects for any changes involving the rights and welfare of subject; before making such change.

R. Islam

80-003

Recd 20/12/79

SECTION 1 - RESEARCH PROTOCOL

1) Title — Gram-negative shock: effect of corticosteroids.

2) Principle Investigators — Dr. R. Islam

Co-investigator — Ward Physicians

3) Starting Date — March 1980

4) Completion Date — March 1982

5) Total Direct Cost — 1st year - $ 78,628.3

2nd year -

6) Availability of Funds

a) Scientific Director's remarks:

b) Controller's remarks:

7) Abstract Summary: The value of corticosteroids for treatment of gram-negative shock is not yet clear despite their extensive use for many years. Approximately 200 cases of gram-negative shock will be studied on random basis in two groups. One group will receive a high dose of corticosteroids along with standard treatment (appropriate fluid replacement and antibiotics) and the other group with only standard treatment alone. Results will be evaluated on the basis of outcome (mortality and morbidity).

8) Review

a) Research Involving Human Subjects _____

b) Research Committee _____

c) Director _____

d) BMRC _____

e) Controller/Administrator _____

SECTION 11 - RESEARCH PLAN

INTRODUCTION:

1. Objective:

The ICDDR,B Treatment Centre receives cases with the clinical picture of gram negative shock. Some of them receive corticosteroids and some do not. Many of them die with or without such treatment. The objective of this study is to find out the differenct etiological causes and improve management. Also to assess whether corticosteroids in therapeutic doses can reduce mortality and morbidity.

2. Background:

Septic shock is characterised by inadequate tissue perfusion usually following bacteremia with gram negative entric bacteria. The patients with shcok frequently continue to detoriate despite intensive therapy to kill the bacteria and restore an effective blood volume. In such circumstances, when a physician uses corticosteroids to treat shock, he can not help but ask whether he is administering "Medical last rites"[1] or a truly beneficial therapy. Even after many studies the usefulness and limitations of these agents remain controversial.

The vaso active phenomenon collectively termed septic shock are probably not only due to gram negative bacilli, the enterobactriacoce (shgella, E.coli, Klebsiella, proteus etc), psuedomonas, minna herellea etc as reported by Leveer in 1972, but are primarily related to the release of endotoxin, lipopolysaccharides or other breakdown products of bacteria into the circulation [2] (Hardaway 1967). Endotoxins exert their major effects on small blood vessels resulting spasm of anterioles and venules leading to significant immobilization of blood in the pulmonary, splanchnic and renal capillaries, organs highly susceptible to endotoxin 11 . Hence experimental evidence suggests that septic shock may be a consequence of both bacteremia as well as endotoxaemia.

Brill and Libman [3] reviewed the first cases of gram negative bacteremia in 1899. They stressed that bloody diarrhoea and vomiting are important parts of the clinical picture. Jacob in 1909, Felty and Keefe in 1924 observed that high fever and marked leucocytosis are associated with gram negative shock. But Waisbren [4] in 1951 was the first to point out that specific shock like picture could be seen in some patients with gram negative bacteremia. Of the 29 cases he studied, 15 exhibited hypotension, cold and clammy skin and lethargy whereas rest had shown more usual toxic manifestations of an acute bacterial infection. McCabe and Jackson [5] observed that older men and women of child bearing age are particularly susceptible to septic shock with mortality 30%-80% and that E.coli was the most common invading organism.

Most of the time patients are alert but complain of a feeling of

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generalised discomfort [5-6], their skin appears mottled, erythematons and may have greyish blue tint, tachycardia, tachypnea and extreme hypotension. Patients often are alert and relatively confortable upto the moment of death [5-6-7].

The value of corticosteroids for the management of gram negative shock is still not clear and debatable despite their extensive use for many years. From the observations until now, it seems that corticosteroids are not the panacea for septic shock but may be useful in selected settings. Corticosteroids are beneficial in shock resulting from or were assqciated with inadequate functions of adrenal gland. With the exception of addisonian crisis, this hypothesis has been disapproved by several studies [8-9], (Gann 1968, Melby 1958). They have estimated plasma cortisol levels and responsiveness in an spectrum of shock status. Adrenal responsiveness to ACTH is not diminished during shock and plasma cortisol levels are often very high in more severe shock [9].

The two instances in the literature where it was observed that the number of patients survived was greater among those who did not receive cortisone either before or during gram negative shock than those who received corticosteroids [5-10].

Shock profoundly alters tissue metabolism both as a consequence of inadequate tissue perfusion and by the toxic effects of endotoxins. Schumer in 1970 [12] studied 50 hypovolaemic shock by volume replacement and sodium bicarbonate to correct acidosis. 50% cases did not respond and remained acedotic and hypovolaemic. These patients were then treated with single dose of dexa-methasone (1 mgm/kg) or saline placebo on random basis as resuscitation continued. Plasma concentration of lactic acid, aminoacids etc returned to normal more rapidly in steroid treated cases (80% recovery to 60% recovery). But number of study patients was too small to be conclusive.

In one well designed study Finland in 1963 [1], reported that there was no evidence of efficacy of corticosteroids. They have used 300 mgm. of hydrocortisone on thefirst day then rapidly reduced this on the following day. This study is often disregarded becaused of the small dose of corticosteroids. Klastersky et al in 1971 [13], observed after using hydrocortisone 2 mgm/kg of betametasone 1 mg/kg, no evidence of benefit from such large doses of corticosteroids. But these studied were criticised from the stand point of design, group size and underlying diseases of the population tested. Nonetheless they seem to balance another study of Weil [14] and Shubin [15], in which they used more than 300 mgm hydrocortisone per day with positive effect on mortality.

Finally from Christy's [16] retrospective analysis of the treatment of septic shock that corticosteroids are useful, the reported data indicates that 90% of patient receiving more than 1 gm of hydrocortisone or its equivalent per day there as only 11% of patients not given this dose survived. A final answer to the question of efficacy of corticosteroids in septic shock awaits a large carefully designed prospective study in which patients are matched to exclude random variable and doses of the drug

are large enough to satisfy all investigators and clinicians. And also to observe whether toxic risks of this agent out weigh their potential benefit. Such a study is of great importance particularly to the developing world since corticosteroids are a very expensive drug provided in wealthy countries, yet are heavily used in poorer countries.

3. Rationale: Since ICDDR,B is the only hospital which takes care most of the diarrhoeal problems, we receive cases where shock despite adequate rehydration from fluid loss due to diarrhoea as measured by blood specific gravity. Inspite of vigorous treatment more than 50% of such cases die in the hospital. The rationale of this study is to improve therapy and determine whether use of corticosteroids can reduce mortality and morbidity.

B. SPECIFIC AIMS:

The specific objectives of this study are to determine:

1. The cause of shock in patients admitted with history of diarrhoea which does not respond to fluid replacement alone.

2. Improved methods of treatment with a standard procedure applicable to developing countries.

3. The role of high dose corticosteroids on mortality and morbidity in such cases of shock.

C. METHODS OF PROCUDRE:

Usually gram negative bacteremia begins abruptly with chills, fever, nausea, vomiting, diarrhoea and prostration. When septic shock develops there are in addition tachycardia, tachypnea, cold and pale extremitis often with peripheral cynanosis, mental obtundation and oligurea. Unexplained hypotension, increased confusion and disorientation may be the only clue to the diagnosis. As shock progresses, oligurea persits, heart failure, respiratory distress and coma supervene. Death usually occurs from pulmonary oedema, generalised anoxaemia, cardiac arythmia, DIC with bleeding menaifestations, cerebral anoxia or combinations of factors.

Appriximately about 200 cases will be studied. Half of these will receive corticosteroids in high doses and the remaining half will not. Both groups will receive a standard treatment.

✓ Selection of patients for study:

1. Unequivocal clinical evidence of shock (BP ≤ 50mm hydystolic) which persits after correction of dehydration as measured by plasma specific gravity.

2. Absence of signs of blood loss

3. No evidence of organic heart disease.

Since therapeutic implications are different and prognosis is considerably better in cases with simple bacteremia than in patients with bacterimic shock only the later category of patients will be considered for study (fever and chills alone will not be a sufficient indication).

Common denominators of therapy for both the groups are:

1. Support of respiration.

2. Maximum fluid administration as guaged by central venous pressure.

3. Antibiotics - ampicillin and gentamycin I.V.[17], other antibiotics may be given according to the sensitivity of bacteria isolated from the blood cultures.

1. Support of Respiration: It is essential to keep the airway clear and administer oxygen.

2. Fluid administration: An adequate circulating blood volume will be achieved with an appropriate electrolyte solution. Bicarbonate containing solutions will be prefered to acetage for correction of acidosis. Oligurea in the presence of hypotension will not be considered as a contradiction for fluid therapy. A central venous pressure measurement will be employed as needed to optimize replacement.

3. Antibiotics: Before starting antibiotics specimens of blood, urine, sputum, catheterised stool and any lesions will be obtained for bacteriological cultures and sensitivities.

After careful cleaning of the skin with iodine, at least 3 blood cultures will be taken. Blood will also be obtained at the same time for electrolytes, urea and creatinine. Pending cultures and sensitivity report, antibiotics will be started on impirical basis. Gentamicin sulphate [15-17] is currently the drug of choice. It is effective more than 95% of common strain of gram negative enteric organisms and arrests staph aureus in the blood. For pseudomonas infection carbenicillin disodium is used in conjunction with gentamicin. For shigella, ampicillin will be used in addition to gentamicin. The fact that renal function is impaired in patients with bacterial shock will be taken into account once the loading dose has been administered. Measurements of serum creatinine concentration provide a basis for estimating the dose and interval of gentamicin. The dose schedule of gentamicin [15-17], is 1.5 mgm/kg. IV initially and 1.5 mgm/kg, IV every 8 hourly. When necessary ampicillin will be used 2 gm , IV initially and 1gm IV every 4 hourly and for salmonella, chloramphanical 1 gm IV initially and 500 mgm every 4 hourly [15]

Dexamethasone phosphate will be used in steroid group in doses of 40 mgm

IV followed by 20 mgm every 4 hourly [15], or hydrocortisone 1 gm IV initially and repeated every 4 hourly for 24 to 48 hours [16].

Blood will be drawn for cortisol level on admission and every 24 hours thereafter. Blood will also be drawn for plasma osmolality. Plasma and urine osmolalities have good correlation in detecting impending renal failure. If urinary osmolality is greater than 400 mOsm and ratio of urine to plasma osnolality is greater than 1.5, renal function is preserved and oligurea is probably due to volume depletion. On the other hand, a urine osmolality of less than 400 mOsm and urine/plasma ratio is less than 1.5 will signify renal failure [18]. Since septic shock is accompanied by maxinal stimulation of L-adrenergic receptors and pressure agents, nor-epenephrine, metaraminal are contraindicated and will not be used [19].

Interpretation will be made to correlate survival rates with, (a) sex, (b) age, (c) underlying disease, (d) etiological organisms and (e) therapeutic factors individually and combined. Patients will be considered survivors if they live longer than 48 hours after heaemodynamic recovery of shock [20].

D. SIGNIFICANCE:

Uptil now we are treating septicaemic shock in different ways, sometime with cortisone (inadequate doses) sometimes without cortisone. We honestly do not know what are the common pathogens responsible in this part of the world. The present study will be a systematic approach to solve this problem so that information thus obtained can have some benefit in the developing world for better management and treatment of patients with gram negative enterotoxaegenic shock.

E. FACILITIES REQUIRED:

No extra office space will be required. Patient will be admitted in the study ward. On an average 5 hospital days per patient will be calculated.

F. COLLABORATIVE ARRANGEMENTS:

None

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FLOW SHEET

48 hrs	24 hrs	16 hrs	8 hrs	4 hrs	0 hrs		
✓	✓	✓	✓	✓	✓	Pulse	
✓	✓	✓	✓	✓	✓	Resp	
✓	✓	✓	✓	✓	✓	Temp	
✓	✓	✓	✓	✓	✓	B.P.	
						Imp.	sensorium
						Not ~~important~~	
						Imp.	Peripheral Cyanosis
						Not ~~important~~	
					✓ 3 samples	Blood C/S	
✓	✓				✓	Blood urea	
✓	✓				✓	Blood creatinin	
✓	✓				✓	Blood electrolyte	
✓	✓				✓	Serum osmo	
✓	✓			✓		T.C. D.C. Hct	
					✓	Stool m/e	
					✓	Stool C/S	
	✓		✓			Urine analysis	
✓	✓					Urine OSM	
						Urine output	
✓	✓				✓	Serum cortisol	

SECTION - 111 BUDGET

A. DETAILED BUDGET

1. Personnel Services:

	Name	Position	%time used	Salary Tk.	Doll
	Dr. R. Islam	Chief Physician & Assoc.Sc.	25%	20,000	
3	Physicians	Physicians	20%	21,600	
5	Study nurse	Sr.Staff nurse	25%	30,000	
1	Veterinarian		5%	2,000	
1	Microbiology techn	Res. Technician	10%	3,000	
1	Clin. Path Tech	Technician	10%	2,000	
1	Biochemistry tech	Res. technician	10%	3,000	
				81,600	

2. Supplies and Materials

Item	Unit cost	Taka	Dollar
Stool culture	200XTk 15.5	31,000	-
ST, LT	200XTk 3	600	-
Blood culture	200X3XTk14.50	8,700	-
Stool microscopy	200XTk 2	400	-
X-ray	200XTk 25	5,000	-
Urine culture	200XTk 7.50	1,500	-
Urine alalysis	200Tk 6.75	1,350	-
completed blood count	200XTk 3X11	6,600	-
Mice	200XTk 3	600	-
Biochemistry (as attached)		17,400	-
Syringe, needled etc		200	-
Medicines -			
Inj. Ampicil-in	200X30X$2.80		16,800

		Tk.	Dollar
Medicines			
Inj gentamicin	200X15X$4,35		13,050
Inj.chloromycetin	50X30X$0.70		1,050
Inj.Oradexon	200X25X$0.75		3,750
Stationary, forms, paper,pencil, etc		2,000	
Misc. items		500	
		77,650	34,650

Biochemistry addendum

Items	Unit cost	Taka	Dollar
Na,K,Cl,Co_2, Sp.gr.	200X3X3	1800	
Sugar	200X3X1.20	720	
Urea & Creatinin	200X3X2.40	1440	
Blood osmolality	200X3X1.20	720	
Urine osmolality	200X3X1.20	720	
Cortisol estimation	200X3X20	12000	
		17400	

3.	Equipments			
	C.V.P. Tray Pharmaseal cat No.30641 (American Hosp.supp.1974)	200X3X$2.75		1650
4.	Patients Hospitalization	200X5X150	150,000	
5.	Out Patient Care	Nil		
6.	CRL Transport	Nil		
7.	Travel & Transportation of persons			
	Local hravel -	1000		
	International Travel			
	Transport (air)			2500
	Per diem			500
	Misc. Regis/Local transport			200
				3200

		Tk.	Dollar
8.	Transport of things Equipments		
9.	Rent, communication & Utilities		
10.	Printing and Reproduction		300
11.	Other contractual services	Nil	
12.	Construction, Rennovation, alteration	Nil	

B. BUDGET SUMMARY

Category		Year 1		Year 2	
		Tk.	$	Tk.	$
1.	Personnel	81.600			
2.	Supplies	77,650	-34650		
3.	Equipment		1650		
4.	Hospitalization	150,000			
5.	Outpatient				
6.	ICDDR,B Transport				
7.	Travel persons	1,000	3200		
8.	Transportation of things				
9.	Rent/communication				
10.	Printing/Reproduction		300		
11.	Contractual service				
12.	Construction				
	TOTAL	310,250	39800		
	30% overhead	93,075	11940		
	Grand Totla	4,03,325	51740		

(Conversion rate $1 = Tk. 15).

26,888.3 + 51740

= $ 78,628.3

SUMMARY

Septic shock is characterised by inadequate tissue perfusion usually following bacteremia with gram negative entric bacteria. The value of corticosteroids for the management of gram negative shock is still not clear and debatable despite their extensive use for many years. For this important issue approximately 200 cases of gram negative shock attending to our cnetre will be studied extensively on random basis in two groups - for the evaluation of the value of corticosteroids in the treatment of shock. One group will receive a high dose of corticosteroids (Dexamethasone) along with standard treatment (fluid, electrolyte replacement and antibiotics). The other groupswill receive standard tratement alone. Ampicillin and gentamicin or in special circumstances chloromycetin will be used intravenously for the control of septicaemia as antibiotics. All possible and necessary investigations including 3 consecutive blood cultures on admission will be done to ascertain the etiological cause of shcok.

Blood will also be drawn for cortosol level estimation on admission and every 24 hours thereafter.

Interpretation will be made to correlate survival rates with (a) sex (b) age (c) underlying diseases (d) etiological organisms and therapeutic factors individually and combined. Patients will be considered survivors if they live longer than 48 hours after haemodynamic recovery of shock.

Patients will receive best possible care and support.

Informed consent will be obtained from the patients or his legal guardian. Confidentiality of records will be maintained.

CONSENT FORM:

This international organisation is dedicated to the cause as well as to better management of diarrhoeal illnesses and its complications. In the present study we want to evaluate the value of corticosteroids in the management of gram negative shock. This is a hormone used in many diseases including shock.

You will receive standard best possible treatment and special care aling with or without corticosteroids.

You have the right to refuse to participate or even withdraw anytime from the study and still you will be cared and receive your treatment.

If you agree to participate in this study, please sign below.

_____

Investigator's signature

_____

Signature or thumb impression of the patient or his legal guardian.

Date : _____

সম্মতি পত্র

উদরাময় রোগের সাধারণ ও জটিল অবস্থায় উন্নততর চিকিৎসা উদ্ভাবনের জন্য এই আন্তর্জাতিক সংস্থা গবেষণায় নিয়োজিত রয়েছে। 'গ্রাম নিগেটিভ' শ্রেণীভুক্ত জীবাণু দ্বারা এক ধরণের বিষ নিঃসৃত হলে রোগীর শরীরে এক মারাত্মক অবস্থার সৃষ্টি হয়। চিকিৎসা শাস্ত্রে ইংরেজীতে একে বলে 'শক্'। এই রোগের চিকিৎসায় কর্টিকোস্টিরোয়েডের বাস্তব উপকারীতা নিরুপণ করবার জন্য আমরা গবেষণা করছি। এই হরমোন শুধু এই রোগে নয়,, অন্য রোগেও ব্যবহৃত হয়।

চিকিৎসাধীন থাকাকালীন আপনার বিশেষ যত্ন নেওয়া হবে এবং চিকিৎসাও আদর্শমান অনুসারে চলবে, তবে আপনার চিকিৎসায় কর্টিকোস্টিরোয়েডের ব্যবহার হতেও পারে আবার নাও হতে পারে।

গবেষণায় অংশগ্রহণ করতে আপনার আপত্তি থাকলে অথবা গবেষণা চলাকালীন কোন সময়ে আপনার উপরে গবেষণা বন্ধ করে দিতে চাইলে আপনি তা করতে পারবেন, তবুও আপনার যথারীতি চিকিৎসার ও যত্নের কোন ত্রুটি হবেনা।

আপনার সম্মতি থাকলে দয়া করে নীচে স্বাক্ষর দিন।

চিকিৎসকের স্বাক্ষর

রোগী কিংবা রোগীর অভিভাবকের স্বাক্ষর অথবা বৃদ্ধাংগুলির ছাপ।

তারিখ----------