Government of the People's Republic of Bangladesh
Office of the principal
Chittagong Medical College
Chittagong, Bangladesh.

Memo No. CMC/PG/2018/ 472 Date: 10/ 11 /2018

To
DR. NAYEMA MASRURA
MD (Neurology)
Student of Part-III
Department of Neurology
Chittagong Medical College.

Subject: Clearance of Research Protocol.

With reference to your application in the above subject, this is to inform you that your research proposal entitled **"EFFICACY OF THIAMINE IN PATIENTS WITH SUSPECTED DRY BERIBERI: AN OPEN LABELED, HOSPITAL BASED STUDY"** has been reviewed and approved by the Ethical Committee of Chittagong Medical College.

(Prof. Pradip Kumar Dutta)
Professor & Head
Department of Nephrology, CMC.
Chairman
Ethical Committee
Chittagong Medical College

(Dr. Nur Hossain Bhuiyan)
Associate Professor & Head
Department of Surgery, CMC
Member- Secretary
Ethical Committee
Chittagong Medical College

Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study

Principal investigator:

Dr. Nayema Masrura
MD (Neurology), 3rd part student,
Department of Neurology,
Chittagong Medical College Hospital.

Guide:

Dr. Md. Hassanuzzaman
FCPS (MEDICINE), MD (NEUROLOGY)
Associate Professor and Head,
Department of Neurology,
Chittagong Medical College Hospital.

Co-Guide:
Dr. Mahbubul Alam Khandakar
FCPS (MEDICINE), MD (NEUROLOGY)
Assistant Professor,
Department of Neurology,
Chittagong Medical College Hospital

The Chairman,

Ethical review Committee,
Chittagong Medical College,
Chittagong.

Subject: Submission of thesis protocol

Sir,

With due respect this is for your kind information that I am a MD (Neurology) 3rd Part student and bound to perform a research work in the respective discipline during my course tenure. Before commencement of a research work however it is mandatory to make it ethically approved, henceforth, I would like to submit my thesis proposal seeking ethical permission. To be more, the title of proposed thesis is "**Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study"** for ethical approval.

I, therefore, pray and hope that you would be kind enough to approve the above to begin my thesis work and oblige thereby.

Faithfully yours

Dr. Nayema Masrura
Student of MD (Neurology) 3rd part
Chittagong Medical College
Chittagong.

APPLICATION FOR ETHICAL REVIEW OF THESIS PROPOSAL
[Application is to be submitted with the thesis proposal and protocol]

Name of the students: Dr. Nayema Masrura

Subject: Neurology **Roll No.** Not applicable	**Course:** MD	**Session:** 2006-07 **Category:** Government

Title: "**Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study"**

Supervisor/ Guide:

Dr. Md. Hassanuzzaman
Associate Professor & Head ,
Department of Neurology,
Chittagong Medical College and Hospital

Co-guide:

Dr. Mahbubul Alam Khandakar
Assistant Professor,
Department of Neurology,
Chittagong Medical College and Hospital

_____

□ 3 hard copies of the thesis proposal and protocol
□ 1 CD of the thesis proposal and protocol
Submission Date: _____
Signature of the Student: _____
For Official Use
Serial No: _____Received on: _____ Reviewed on:_____
Comment:_____

Member-Secretary ERB Chairperson ERB

CMC Ethical Review Committee

Chittagong Medical College
Chittagong 4203, Bangladesh
Tel: 619400 Fax: 630180 Email: cmc@fnfbd.net

(Application for Ethical Clearance for Studies for Post Graduate Thesis proposal)

1**. Name of the applicant**: Dr. Nayema Masrura

2. **Course**: MD (Neurology)

3. **Category**: Government

4. **Title of the study:** "**Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study"**

5. **Type of the study**: A Quasi experimental study.

6. **Duration**: Twelve (12) months

7. **Any collaboration**: This study will be conducted in neurology department in collaboration with department of Internal medicine, Chittagong medical College Hospital.

8. **Conflict of interest disclaiming**: Not applicable

9**. Supervisor:**

Dr. Md. Hassanuzzaman
Professor & Head
Department of Neurology,
Chittagong Medical College Hospital.

Co-guide:

Dr. Mahbubur Alam Khandakar
Assistant Professor
Department of Neurology,
Chittagong Medical College Hospital10.

10. **Abstract of study:** Attached here with.

Put ✓ mark the appropriate answer to each of the following (If not Applicable write NA)

1. Source Population:			**4. Are subjects clearly informed about:**		
(a) Ill Subjects	✓Yes	No	(a) Nature and purpose of the study	✓Yes	No
(b) Non ill subjects	Yes	✓No	(b) Procedures to be followed including alternatives used	✓Yes	No
(c) Minors or persons under guardianship	Yes	✓No	(c) Physical risks	✓Yes	No
2. Does the study involve:	Yes	No	(d) Private questions?	✓Yes	No
(a) Physical risks to subjects	Yes	✓No	(e) Invasion of the Body	✓Yes	No
(b) Social risks	Yes	✓No	(f) Benefits to be derived	✓Yes	No
(c) Psychological risks to subjects	Yes	✓No	(g) Right to refuse to participate or withdraw from the study	✓Yes	No
(d) Discomfort to subjects	Yes	✓No	(h) Confidential handling of data	✓Yes	No
(e) Invasion of the body	✓Yes	No	(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure	✓Yes	No
(f) Invasion of privacy	Yes	✓No	**5. Will signed consent/verbal consent be required**		
(g) Disclosure of information damaging to subject or others	Yes	✓No	(a) From Subject	✓Yes	No
3. Does study involve:			(b) From parents or Guardians	✓Yes	No
a) use of records (hospital, medical, death,birth or other)	Yes	✓No	**6. Will precautions be taken to protect anonymity of subjects**	✓Yes	No
b) use of fetal tissue or abortus	Yes	✓No			
c) use of organs or body fluid	Yes	✓No			

Check documents being submitted herewith to committee

Abstract:

Umbrella proposal initially:

Protocol and CRF:

Informed consent form for subjects:

Informed consent form for parents:

Verbal consent form for subjects:

Procedure for maintaining confidentiality:

Schedule of the study

Declaration

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

Dr. Nayema Masura
MD (Neurology) 3rd Part
Department of neurology,
Chittagong Medical College.

Forwarding of the Guide/Supervisor

This is to certify that Dr. Nayema Masrura, is proposed to carry out research work titled "**Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study"** and prepared this research proposal under my direct supervision.

Dr. Md. Hassanuzzaman
FCPS (MEDICINE), MD (NEUROLOGY
Associate Professor & Head
Department of Neurology,
Chittagong Medical College and Hospital

Chittagong Medical College
Research cell
Chittagong- 4000, Bangladesh
Tel-619400, fax-630180, E-mail: cmc@fnfbd.net

Research Proposal
For postgraduate Thesis/Dissertation

Part—A

1. Thesis title : "**Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An open labeled Hospital Based Study"**

2. Student's name : Dr. Nayema Masrura

3. Course : MD (Neurology)

4. Place of study : Chittagong

5. Duration : 12 Month

6. Date of commencement: July 2018

7. Date of completion: June 2019

8. Sponsoring agencies: not applicable

9. Total cost : Tk. 250,000/ (Two hundred and fifty thousand only)

10. Other support for proposed research:

(i) Is this research being supported by any other source?-NO

(ii) Has an application for funding of this project been submitted to any other organization?-NO

11. Date of submission: 02/05/2018

12. Signature of the student: 

13. Signature of the Guide: 

14. Signature of Course Co-ordinator: 

PART-B

STUDENT'S INFORMATION SHEET

1. (i) Name**:** Dr. Nayema Masrura

(ii) Designation**:** MD Neurology Student

(iii) Official Address with telephone**:**

Ward: 18, Neurology Department,

Chittagong Medical College, Chittagong,

(iv) Present Residential Address with telephone**:**

94/A, Santibug R/A, Chotopole,North Agrabad, Ctg

Mobile No- 01817743838

2 .Academic Background**:**

Degree	Institute	Board/University	Result	year
MBBS	Chittagong Medical College	Chittagong university	Pass	2004
HSC	Chittagong College	Chittagong board	1st division	1997
SSC	Chittgong Port Authority Girls'High School	Comilla board	1st division	1995

3. Field of Specialty**:** Neurology

4. (a) Research Experience**:** N/A

(b) Other Experience: Nil

5. Percentage of time to be devoted to this project**:** Full time

6. Number of Scientific Publications**:** Nil

Part-C

Abstract:

In our day to day clinical practice we have encountered many of them with neurological complaints mimicking thiamine deficiency (TD). Investigations to confirm this condition are not available in our setting. So, the diagnosis of TD in such contexts is a real challenge and a high level of clinical suspicion should be demonstrated in such situations. Early treatment with thiamine has the potential to rapidly reverse clinical signs and minimize sequelae, before the onset of fixed lesions. The lack of diagnostic capacity in our settings justifies the use of a therapeutic thiamine challenge in cases with high clinical suspicion. However, there is paucity of study about the clinical spectrum and therapeutic response of such patients in Bangladesh. The aim of this prospective hospital based quasi-experimental study will be to determine the clinical pattern of patients with suspected dry beriberi and their outcome to thiamine therapeutic challenge in our setting. Fifty-five patients of clinically suspected dry beriberi will be enrolled as per inclusion and exclusion criteria. Then therapeutic trial of Inj. Thiamine will be given IV for 1st week (200mg IV daily for peripheral neuropathy and then orally (tab. Thiamin 100mg bd) for 11 weeks. Patients will be followed up after 1, 6 and 12 week to see the response. Pre and post treatment data will be recorded in pre designed case record form. To determine whether any of the difference between pretreatment and post treatment values were statistically significant or not, either Friedman's test or Cochran's Q test were used. Former test compares the quantitative variables and non-dichotomous qualititative variables and the later test compares the dichotomous qualitative/categorical variables. Statistical significance were defined as $P < 0.05$ and confidence interval was set at 95% level. Analysis will be performed with SPSS version 23. Our study result is likely to sensitize the health professionals of this region about this neglected health issue by increasing awareness of the clinical spectrum of Thiamine Deficiency related Peripheral Neuropathy. Moreover, study may provide the impetus for fashioning national policies on the diagnosis, treatment and prevention of thiamine deficiency disorders in our country.

Part-D

1. Introduction:

According to World Health Organization (WHO) International Nomenclature of Diseases, Thiamine deficiency (TD) syndrome is a clinical syndrome that arises insidiously as a result of a severe, prolonged deficiency of thiamine in the diet, manifested in the initial stages by anorexia, malaise, and weakness of the legs, frequently with paraesthesia; there may be slight oedema and palpitations. The disorder may persist in this chronic state or may at any time progress to an acute condition characterized either by cardiac involvement with oedema or by peripheral neuropathy; forms intermediate between these two extremes may also occur. It is thought that the basic cause is the inhibition of a series of enzyme-catalysed cleavages of carbon-carbon bonds in which thiamine diphosphate is a coenzyme. Commonly used synonyms are beriberi; Ceylon sickness; occidental beriberi (in part); oriental beriberi (in part); rice disease etc. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi), but may also arise if highly refined wheat flour forms a major part of the diet, in alcholics, and in food faddists (occidental beriberi).[1]

Thiamin (vitamin B1) is widely distributed in foods of both vegetable and animal origin. It is an essential micronutrient with dual coenzymatic and non-coenzymatic functions. It is involved in carbohydrate and branched-chain amino acid metabolism, as well as in the production of neurotransmitters, myelin, and nucleic acids. There is also evidence that thiamine plays a role in immune and anti-inflammatory processes and gene regulation.[2-5]

The human body requirement for thiamine is exclusively dependent on regular dietary intake, as there is no significant mechanism for endogenous production of thiamine or for prolonged storage of thiamine in the human body. It is estimated that the body can store thiamine for 2–3 weeks. Staple diets that are deficient in thiamine would result in low body thiamine levels, which may be subclinical or may manifest as a thiamine-deficiency syndrome. Thiamine deficiency is classically associated with diets consisting mainly of

milled white cereals, particularly polished rice and highly refined wheat flour. Milling significantly reduces the thiamine content of cereals: the thiamine content of highly milled white rice is 0.08 mg/100 g compared with 0.33 mg in unmilled brown rice. Rice washing and cooking methods may result in additional losses of up to 45–60% of thiamine. Rice is the most important food source in our country. The combination of limited body storage and a high turnover rate (half-life <10 days) results in potential depletion of thiamine stores within 2 weeks if it is not continuously replaced. In addition, thiamine's hydrosolubility, coupled with its renal clearance profile, contributes to a propensity to thiamine deficiency (TD) throughout life.[1,6]

It principally affects precarious communities where children and adults are most vulnerable and where dietary habits rely on refined processed cereals or tubers (e.g., rice, wheat, cassava), notably in Southeast Asia and Africa. TD can result from various mechanisms that are not mutually exclusive. The most frequent mechanisms are insufficiency of dietary thiamine (enteral–parenteral supply) and poor intestinal absorptive capacity during malnutrition, tropical enteropathy, or secondary to surgical resection of large portions of the gastrointestinal tract. A relative inadequacy of thiamine content to caloric ratio (high carbohydrate diets) is also common. It is this thiamine–calorie imbalance that is responsible for TD in heavy drinkers of sweet drinks and contributes to the onset of TD when dextrose-based fluids are administered without thiamine supplementation in critically ill patients. Poor thiamine intake may be due to losses from food secondary to pre-cooking and food processing (e.g., repetitive rice washing), a restrictive diet due to cultural habits and ingestion of antithiamine factors (tea leaves, betel nuts, and coffee) or thiaminases (e.g., fermented raw fish, mycotoxins, stored food, and larvae) that break down and, thus, inactivate thiamine. Excessive loss of thiamine from the body, such as renal (loop diuretics, osmotic diabetic diuresis) or digestive losses (chronic diarrhea, hyperemesis), can also precipitate TD. At cellular level, two main mechanisms contribute to TD – impaired uptake or increased demand. Impaired cellular uptake of thiamine can be due to defects in thiamine transporters or specific enzymes (mutation, hypomagnesemia, drug-induced interaction), or reduced

levels of ThDP. Increased cellular demand of thiamine occurs in hypermetabolic states during critical illness, e.g., severe infections, shock, burns, fever, hyperthyroidism. Exposure to toxic substances, such as alcohol can also affect thiamine metabolism. When this occurs during pregnancy, the fetus may be indirectly affected, as observed in fetal alcohol syndrome. Maternal TD associated with excessive alcohol consumption is usually secondary to inadequate thiamine intake or decreased intestinal absorption due to reduced expression of ThTr-1. In addition, impaired intracellular thiamine utilization affecting the TPK activity results in a low bioavailability of the active cellular ThDP due to ethanol and acetaldehyde exposure. In humanitarian fields, TD occurring in epidemic proportions has been described following abrupt food shortage caused by disasters, famines, conflicts, or large population displacement.[7]

TD in adult may be be manifestated in three forms: TD with peripheral neuropathy, TD with cardiomyopathy and TD with lactic acidosis. TD with peripheral neuropathy is an acute form of thiamine deficiency characterized by polyneuropathy with paraesthesia of the extremities (especially the legs), reduced knee jerk and other tendon reflexes, and progressive severe weakness and wasting of muscles; the susceptibility to infections is greatly increased. Synonyms are atrophic beriberi; dietetic neuritis (in part); dry beriberi; endemic polyneuritis; panneuritis endemica; paralytic beriberi; polyneuritis endemica. The neurological signs constitute dry beriberi are evident even in the early stages. Polyneuritis and paralysis of the periphgeral nerve predominate; the central nervous system is scarcely involved. Manifestations are seen in the autonomic, sensory and motor systems. The autonomic nervous system is functionally altered in the early course of disease, as the clinical and pharmacological findings in beriberi patients suggest. In the sensory system, tactile sensation is the first affected, then there is pain, and finally temperature sensitivity altered. The sensory disturbances are usually not so marked as to be termed ‘anesthesia’, but superficial hyperesthesia is more or less characteristically distributed, beginning in the lower extremities, finger tips, lower abdomen and perioral

areas and gradually expanding. The sensory effects are usually symmetrical although the side that is greater use tends to be affected first. Paraesthesia is often the earliest sign of diminished sensitibility and the patients complains of burning sensation in the legs and toes. Although rare, sensory disturbances of the oral cavity are encountered in a few cases. Paralysis of the motor nerves occurs after the sensory disturbances. This also begins in the tips of the lower extremities, then in the fingers, and ascends progressively. There is increasing muscular weakness which is readily demonstrated by the inability of the individual to rise from a squatting position without assistance and, as the disease progresses, there is atrophy of the leg muscles. The tendon reflexes are also affected especially with loss of ankle and knee jerks. Painful calf muscles and, eventually, foot drop and, later, wrist drop may also develop. Advanced neurological changes may result in great difficulty in walking and may even lead to complete paralysis. Frequently, vertigo and instability of the body during walking are noted in beriberi patients. The shaky gait is equivalent to positive Romberg's sign and mostly caused by impaired vestibular function in advanced cases although it is partially due to decrease deep sensations. Nystagmus, as a sign of manifestation of vestibular malfunction, has been reported to occur particularly in alcoholics who developed Wernick's encephalopathy. [1,6]

Epidemics of beriberi manifesting with sensory neuropathy and gait ataxia have been described in children and adults within segments of the African population subsisting on diets that provide marginal or submarginal intakes of thiamine[8] in prison populations[9,10] and in garrisoned troops.[11] Seasonal ataxic syndrome is an acute thiamine deficiency state that has occurred in epidemics in parts of Western Nigeria during the rainy season and manifested with clinical features of Wernicke's encephalopathy. Studies have confirmed that seasonal ataxic syndrome is a thiamine-deficiency disorder that occurs in low-income individuals with marginal thiamine deficiency. Tropical ataxic neuropathy (TAN) is a syndrome of sensory polyneuropathy, sensory ataxia, bilateral optic atrophy, and bilateral sensorineural deafness described in several African countries. The cardinal clinicalfeatures of TAN are similar to those of thiamine deficiency.[12] A therapeutic trial of thiamine in these patients has indicated that it is a thiamine deficiency state.[13]

Besides there are some clinical conditions which may probably be results from TD. There are some neurologic syndromes of undetermined etiology occurring in parts of Africa that are probable thiamine-deficiency syndromes but have not been conclusively investigated and confirmed to be due to thiamine deficiency. One of these is epidemic spastic paraparesis (konzo), a severely debilitating disorder characterized by abrupt onset of paraplegia occurring in patients subsisting almost exclusively on a diet of improperly processed cassava roots.[14] Epidemics have been reported from several countries in Central and East Africa affecting hundreds of thousands of people, predominantly children and young women. The etiology remains unknown, but several aspects of the clinical presentation are suggestive of a thiamine-deficiency disorder.[12] Thiamine levels have never been tested in these patients, and at herapeutic trial of thiamine has never been performed. Another probable thiamine-deficiency disorder is the epidemic optic neuropathy associated with peripheral neuropathy, which has been reported in Tanzania and Somalia.[15,16] The clinical description of the syndrome is quite similar to the epidemic of optic and peripheral neuropathy described in Cuba, where patients were found to be thiamine deficient and responded to vitamin B supplementation.[17] The epidemic optic neuropathy syndrome may well be a forme fruste of TAN, which also presents with optic neuropathy and peripheral neuropathy. Although acute cases of epidemic optic neuropathy have been successfully treated with vitamin B supplementation in Tanzania,[16] thiamine levels have never been tested in these patients, and a therapeutic trial of thiamine has never been conducted.

Thiamine deficiency can be investigated using plasma, erythrocytes, whole blood ThPP levels and urinary excretion of thiamine before and after exogenous thiamine administration.[18] However, serum or whole blood thiamine has poor sensitivity and specificity in severe acute conditions as it decreases during systemic inflammation, and represents only a small part of the whole body thiamine pool. Erythrocyte transketolase activity more accurately evaluates the thiamine status of the body and is, therefore, used

as standard.[19] MR imaging showing specific lesions can also be very helpful in early detection of neurologic features of TD in children. However, none of these investigations allow immediate diagnosis of TD in life-threatening conditions and they are rarely available in resource-limited settings. Consequently, the diagnosis of TD in such contexts is a real challenge, especially considering its wide and non-specific clinical spectrum and potentially fatal prognosis. A high level of clinical suspicion should be demonstrated in the following situations: suspicion of infantile beriberi; unexplained neurological signs, encephalitis, and cardiac failure; early clinical deterioration after initiation of feeds in malnutrition; sepsis (including in SAM); severe burns; major trauma; hypoxia; and unresponsive lactic acidosis. However, in the absence of specific diagnostic tests, the only way to diagnose TD is to carry out a therapeutic thiamine challenge. Considering its safety profile and wide dosage range, in such cases, thiamine can be administered by slow intravenous injection over 30 min. In severe acute conditions caused by TD, rapid clinical improvement will be seen (within hours or days) following thiamine administration.[7]

Thiamine deficiency global prevalence is poorly documented. Despite being easily treatable, TD continues to be seen in all age groups in both high and low resource countries with potentially severe and life-threatening consequences.[7] Chittagong Medical College Hospital is the second largest tertiary level hospital in Bangladesh. It provides different specialist service mostly to the patients of south-eastern part of Bangladesh. It has a rich Neurology department. In our clinical practice we have encountered patients especially from Satkania, Bashkhali, Cox'sbazar, Teknaf, Saintmartin, Mosheskhali upazillas of Chittagong Division with neurological features mimicking TD. Most of them are from low socio-economic strata. They are at risk of developing TD syndrome for their dietary habit. In our experience most of them show positive response to therapeutic trial of thiamine. However, there is paucity of any survey or systemic study in this issue. This situation has stimulated us to design this study to evaluate the clinico-epidemiological features of these patients and to assess their response to thiamine trial in a systematic way.

2.Research questions:

- What is the clinic-epidemiological profile of adult patients with suspected dry beriberi ?
- How do they response to therapeutic thiamine challenge?

3. Objectives:

3.1 General objective:

- To evaluate the efficacy of Thiamine in patients with suspected / possible dry beriberi

3.2 Specific objectives:

1. To describe the socio-demographic profile of patients
2. To categorize the patients according to their presenting symptoms and signs.
3. To assess and compare pre and post treatment neurological features

4. Rationale:

A vast population of southern area of Chittagong division of Bangladesh (Satkania, Bashkhaki, Cox'sbazar, Teknaf, Moheshkhali, Saint martin) are at risk of developing thiamine deficiency syndrome due to their dietary habit and low socio-economic condition. In our day to day clinical practice we have encountered many of them with neurological complaints mimicking thiamine deficiency (TD). However, TD has a large clinical spectrum, and as such it is frequently misdiagnosed, sometimes with fatal consequences or permanent neurological sequelae. TD can be investigated using plasma, erythrocytes, whole blood ThPP levels, and urinary excretion of thiamine before and after exogenous thiamine administration. But none of these investigations allow immediate diagnosis of TD in life-threatening conditions and they are rarely available in resource-limited settings. So, the diagnosis of TD in such contexts is a real challenge and a high level of clinical suspicion should be demonstrated in such situations. Early treatment with thiamine has the potential to rapidly reverse clinical signs and minimize sequelae, before the onset of fixed lesions. The lack of diagnostic capacity in our settings justifies the use of a therapeutic thiamine challenge in cases with high clinical suspicion. It is an effective, inexpensive, and easy to administer medication.

This issue of dry beriberi has got less attention and in our extensive literature search we have failed to identify any document related to dry beriberi in this part of Bangladesh. So, it is rational to design a prospective study to determine the clinical pattern of patients with suspected dry beriberi and their outcome to thiamine therapeutic challenge in our setting. Our study result is likely to sensitize the health professionals of this region about this neglected health issue by increasing awareness of the clinical spectrum of TD. Moreover, study may provide the impetus for fashioning national policies on the diagnosis, treatment and prevention of thiamine deficiency disorders in our country.

5. Metarials and methods:

5.1 Type of study: Quasi-experimental study, self –controlled clinical trial (pretest – posttest design)

5.2. Period of study: One year.

5.3. Place of study: Department of Neurology, Department of Medicine of Chittagong Medical College Hospital.

5.4. Study population: All the patients admitted in the above mentioned ward of CMCH with clinical diagnosis of suspected dry beriberi.

5.5. Sampling technique: Required number of patients will be selected purposively as per set criteria

5.6. Eligibility criteria:

Inclusion criteria:

1. Any person admitted to CMCH as a Suspected/Possible dry-beriberi.

Risk factors + at least 2 of the following signs:

Risk factors include Imbalanced diet (diet poor in thiamine/rich in carbohydrate or anti-thiamine factors)**,** malnutrition, alcoholism, GIT surgery, chronic diarrhoea, chronic vomiting, pregnancy or history of recent delivery, chronic. diuretics use, renal dialysis, total parenteral nutrition.

a) Muscle weakness of upper and or lower limb (less than grade 5 power in MRC scale)
b) Positive sensory symptoms (burning, tingling or pain)
c) Objective sensory deficit (pain, touch, position, vibration sense)
d) Absent or reduced deep tendon reflexes
e) Positive squat test (unable to rise after squatting without help)
f) Leg swelling

2. Age 18 years and above

Exclusion criteria:

1. Patients with isolated cardiac/wet beriberi
2. Patient with known causes of peripheral neuropathy such as Diabetic, hereditary, Demyelinating (GBS, CIDP), metabolic (hepatic/renal impairment), drugs (e.g. INH, Ethambutol, Phenytoin, Metronidazole, Dapsone etc.) Toxin (As ,OPC, Pb ,Hg except alcohol) etc.
3. Patients refuse to participate

5.7. Sample size:

To estimate the prevalence following formula will be used to determine the sample size by doing finite population correction:

$$n = \frac{z^2 pqN}{d^2 \times (N-1) + z^2 pq}$$

Where,

n= required sample size,

z= z-value of standard normal distribution at a given level of significance

p=prevalence of the event (Prevalence of clinically suspected dry beriberi patients show positive response to thiamine trial, usually from previous study)

q=100-p

d= allowable error/precision in the estimate of 'p'= usually 10% of p

N= Expected number of suspected dry-beriberi patients admitted in Neurology and Medicine department of CMCH during data collection period.

Here,

z= 1.96 at 95% confidence level

p=80%=0.8[Prevalence of clinically suspected dry beriberi patients show positive response to thiamine trial is not available from extensive literature search. However, from our experience, 80% of these patients show positive response].

q= (100-80) %=20%=0.2

d=10% of p= .1×.7=.08

N= 75

$$\text{So, } n = \frac{1.96^2 \times 0.8 \times 0.2 \times 75}{(.08)^2 \times (75-1) + 1.96^2 \times 0.8 \times 0.2} = 41.6 \approx 42$$

However, final sample size will be increased to 55 assuming 30% drop out.

5.8. Data collection tool:

- A predesigned Case Record Form.

5.9. Procedure of collecting data:

All patients attending the above mentioned ward with a diagnosis of suspected dry beriberi will be assessed for eligibility. Informed written consent will be obtained from the patients or attendants after full explanation of the ultimate outcome, complications and purpose of the study. They will be informed of their right to withdraw from the study at any stage. After consenting, the details of the patient's history including demographic information, food habit, clinical findings at presentation, results of laboratory, and neuroimaging testing will be recorded in case record form. A general physical examination (e.g. pulse, blood pressure, respiratory rate), neurological examination (higher mental function, cranial nerves, Motor, sensory, cerebellar function), results of laboratory and electro-diagnostic testing (if necessary) were recorded in case record form. Then therapeutic trial of Inj. Thiamine is given IV for 1st week (200mg IV daily) then orally (tab. Thiamin 100mg bd) for 12 weeks. Patients will be followed up after 1, 6 and 12 week to see the response.

5.10. Data analysis:

All the data will be checked and edited after collection. Continuous data will be reported as the means ± SD or median and itraquartile range. Qualitative or categorical data will be described as frequencies and proportions. Proportions will be compared using chi-square or Fisher's exact test whichever will be applicable. To determine whether any of the difference between pretreatment and post treatment values were statistically significant or not, either Friedman's test or Cochran's Q test were used. Former test compares the quantitative variables and non-dichotomous qualititative variables and the later test compares the dichotomous qualitative/categorical variables. Statistical significance will be defined as $P < 0.05$ and confidence interval will be set at 95% level. SPSS (Statistical Package for Social Science) for Windows version 23 software will be used for the analyses.

5.11. Variables under study:

Primary Outcome Variable:

1. Treatment response measured by Overall Neuropathy Limitation Scale (ONLS) score before and after treatment.

Secondary Outcome Variables:

1. Comparison and Assessment of clinical features at presentation and after treatment: leg swelling, muscle cramp, muscle power (MRC grading), deep tendon reflexes, sensory impairments (tingling /burning /pain/ touch/ position /vibration), squat test.

5.12 Operational definition:

Risk factors: Imbalanced diet (diet poor in thiamine/rich in anti-thiamine factors)**,** malnutrition, alcoholism, GIT surgery, chronic diarrhora, chronic vomiting ,pregnancy, diuretics, renal dialysis, total parenteral nutrition.

Anti-Thiamine factors: Raw or fermented fish,shell fish,ferns, Tea, coffee, betel nuts

Possible/suspected dry beriberi: Risk factors + at **l**east 2 of the following signs:

a) Muscle weakness of upper and or lower limb (less than grade 5 power in MRC scale)
b) Positive sensory symptoms (burning, tingling or pain)
c) Objective sensory deficit (pain, touch, position, vibration sense)
d) Absent or reduced deep tendon reflexes
e) Positive squat test (unable to rise after squatting without help)
f) Leg swelling

Probable dry beriberi: Above symptoms recovered after thiamine treatment.

Socio-economic status: It will be measured as per Modified Kuppuswamy Socio-economic scale (Appendix-A) and grouped into five categories :Upper class, Upper middle class, Lower middle class, Upper lower class and Lower class.

5.14. Utilization of results:

This study result will be helpful to formulate a guideline for the management of suspected case of dry beriberi in our setting and improve the outcome of beriberi by reducing over or under treatment. Further research on such procedure can be designed by utilizing the results of this study.

6. Facilities:

Administrative setup and resource persons are available in the study site.

7. Approval of the head of the research cell and ERC:

Under consideration.

8. Clarification of the ethical issue:

1. Voluntary consent will be taken from each patient to be enrolled for the forthcoming study. patient's legal guardian will be approached where required.

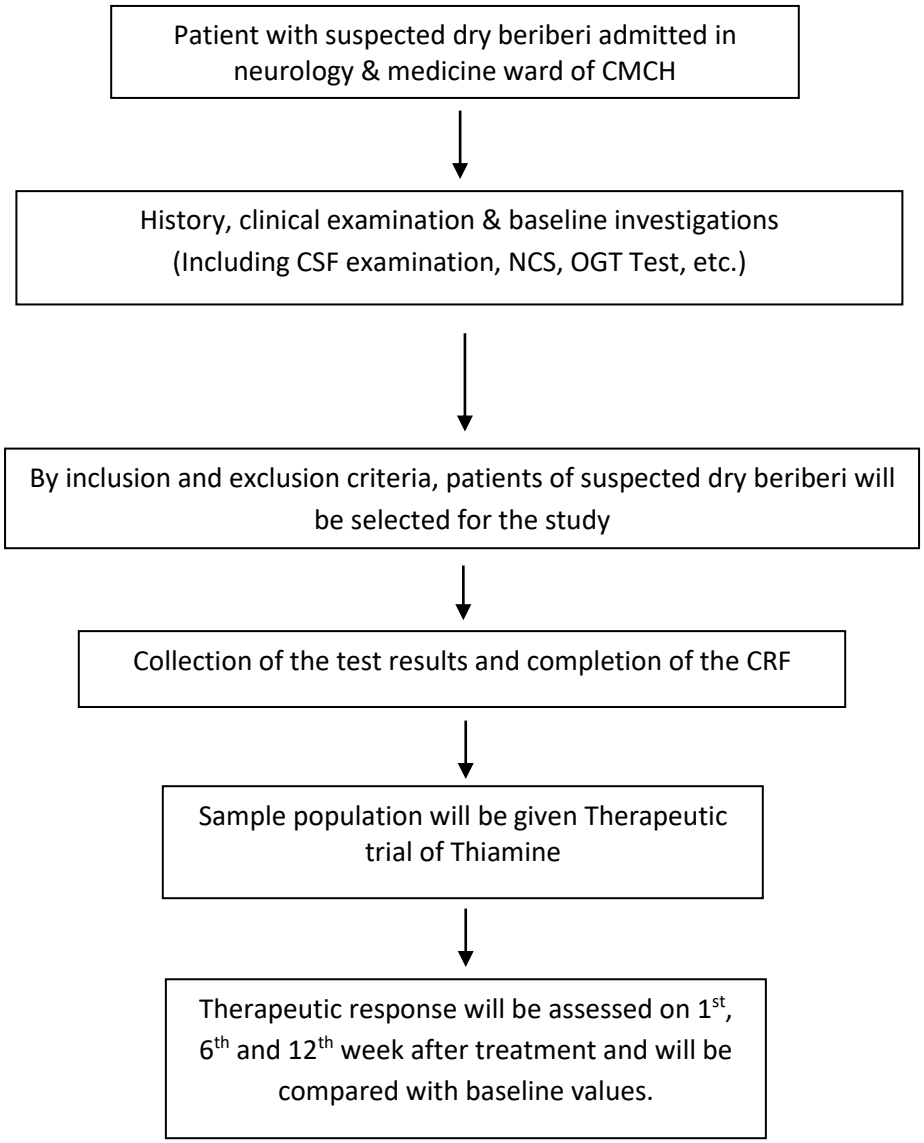
2. All measures will be taken to preserve patients' anonymity and privacy. To do such, a separate case record form (CRF) will be utilized for every patient issuing a different identity code and only principal investigator will have access to patients' data. To be more, personal information of any of them will not be handed over any third party without their consent.

3. Evaluation of each research participant will be done thoroughly. Required investigations including radio-imaging and biochemical tests will be done in the CMCH if facilities available.

4.They will be treated as per treatment guideline for the disease of research interest. Importantly, no financial support will be provided to any research participant for being a subject in the research work.

5. All patients' will be informed about the nature and purpose of the study. They will get informed that their participation in the coming study research will not only benefit them but also the whole community as well.

5.13. Flow Chart of Study Design:



5.15 Time schedule:

	item	July to August 2018	September to October 2018	November 2018 to April 2019	May 2018	June 2019
1	Literature search & protocol writing					
2	Piloting & CRF(Case record form) Finalization					
3	Data collection					
4	Data entry					
5	Data analysis					
6	Report writing					
7	submission					

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PART –E

BUDGET

I. Total Budget: 2,50,000 bdt (Two lacs and fifty thousand taka only)

II. Detailed Budget:

1. Personnel cost: Not Applicable.

2. Field Expenses/ Laboratory Costs: 1,50,000.

3. Supplies and Materials:

4. Patient Cost (if applicable): Transport fee 55,000.

5. Travel cost (Internal travel cost only) : 5000.

6. Transportation of Goods: Not Applicable.

7. Office Stationary: Internet 5000

   Stationary 5000

   Photocopy 5000.

8. Data Processing/ Computer Charges: 15,000.

9. Printing and Reproduction: 10,000.

10. Contractual Services (other than manpower): Not Applicable.

11. Administrative Overhead: Not Applicable.

12. Miscellaneous: Not Applicable.

PART –F

Informed Consent Form

Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An Open Labeled Hospital Based Study.

After being fully informed about the objectives ,consequences of the study and any right to withdraw myself from the study at any time for any purpose what so ever, I am……Here by giving consent to participate in the study conducted by Dr.Nayema Masrura, (Neurology) thesis part student, CMCH.

I fully recognize that my participation in this study will generate valuable medical information that might be used for the interest of patients in future.

In this research if any adverse effects of drugs are found investigators will take immediate measures for treatment.

I shall try my best comply with the instruction given by the investigator throughout the whole period of study.

Signature/Thumb impression of the patient's guardian Date……	Signature/Thumb impression of the Subject Date……
Signature/Thumb impression of the Investigator Date……	Signature/Thumb impression of the Witness Date……

PATIENT **INFORMATION SHEET**

Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An Open Labeled Hospital Based Study.

Introduction:

Beriberi is a severe form of Thiamine (vitamin B1) deficiency. Historically it is prevalent in countries which use polished rice as staple food. Disease is manifested by muscle weakness, difficulty in walking, leg swelling, heart failure, unusual tiredness, memory loss, anorexia, nausea etc. Diets rich in Thiamine are pulse, beef, liver, dried milk, nuts, oats, oranges, pork, eggs, seeds, legumes, peas and yeast. Foods are also fortified with thiamine. Some foods that are often fortified with B1 are rice, pasta, breads, cereals and flour.

Procedure for objective:

This research will be conducted by the department of Neurology, CMCH. If you are agreed to take part in this research, then the researcher doctor will ask you some relevant questions.

Risk of the research: no known risk.

Advantages for participate in the research:

If you participate in the research, then you may be benefited directly. You will get the chance of proper diagnosis and treatment. This research will help the Bangladeshi doctors to know more about the disease. This research may be useful for a large number of people of the country.

Expenditure:

For participation in this research you have no expense or payment.

Confidentiality:

Confidentiality will be strictly maintained for all information during and after the research. You will be given an ID number for follow up. All of your information will be kept under lock and key in the office file cabinet. Personal information will not be used for any analysis, research or publication and will not be revealed to anyone except the researchers. As a result none can know your personal information.

Voluntary participation:

Participation in the research is completely voluntary. You can refuse to participate in the research or withdraw yourself from the research any time after participation. Signing in this consent form will not hamper your any legal rights.

Queries: If any query, contact with the researcher Dr. Nayema Masrura, Mobile 01707743838, Department of Neurology, CMCH.

PART-G

CASE RECORD FORM

Title: Efficacy of Thiamine in Patients with Clinically Suspected Dry Beriberi: An Open Labeled Hospital Based Study.

ID no: Ward No: Bed no: Reg. No:

Date of admission: Date of Discharge:

Date of inclusion in study:

Contact No: Address:

Particulars of the Patient:

1. Name:
2. Age (in years):
3. Sex: Male=1/Female=2.
4. Religion: Muslim=1/ Hindu=2/Buddist=3 / Christian=3
5. Marital Status: Married=1/ Unmarried=2/ widow=3/divorced=4.
6. Residence: urban=1/ semi urban=2/rural=3/others=4(specify).
7. Education:
8. Occupation:
9. Monthly Income:
10. Food Habit:
    a) Rice eaten: Polished un-boiled=1/polished boiled=2
    b) Washing before cooking: …….times
    c) Discarding excess water after cooking: no=1/yes=2.
    d) No of meals per day:

e) Contents of major meals:

Breakfast	Snacks	Lunch	Afternoon Snacks	Dinner

f) Anti-thiamine food intake: Betel nut/ tea/ fermented fish/shell fish.

…….min after major meal,……..times per day

11. Alcohol intake:

Duration…….years, Amount:……/day

current alcohol user=1/ former alcohol user=2/ never alcohol user=3.

12. Other associated conditions (if any):

GIT surgery/ Chr. Diarrhoea/ Chr. Vomitting/Renal disease/ cancer/ pregnancy/others (specify):

13. No of childbirth (in females):

Time of last childbirth:

Duration of Lactation:

12. Presenting Symptoms:

12.1) Limb Weakness: Upper limb/ lower limb/ both. Duration:……..days

12.2) Leg swelling: yes/ no. Duration……..days

Nil=0, Mild=+, moderate=++, severe=+++

12.3) Sensory Impairment (pain, tingling, numbness): yes/ no. Duration: ……. Days.

12.4) anorexia , nausea : yes/ no. Duration: ……. Days.

12.5) Muscle cramp: no/mild/moderate/severe. Duration: ……. Days.

12.6) other symptoms (specify): Duration: ……. Days.

13. Physical Examination:

13.1) Height: ……., weight:…….Kg, BMI (weight/height$^{2)}$:

13.2) Mid Upper Arm Circumference(MUAC):……cm

13.3) Anaemia: Absent/ Present.

13.4) muscle power (MMRC Grading):

Upper Limb	**Lower Limb**
Proximal:	Proximal:
Distal:	Distal:

13.5) deep tendon reflexes: normal =0, Diminished=1, Absent=2

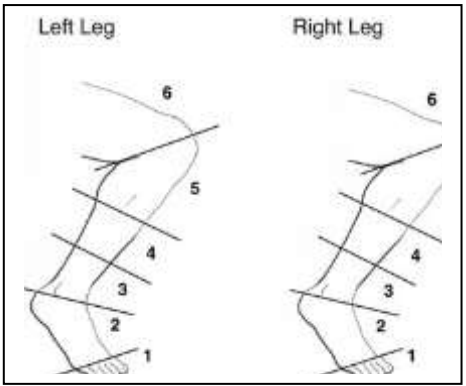
	Biceps	Triceps	Supinator	Knee	Ankle	Planter
Right						
Left						

13.6) Squat test: negative=0/ positive=1.

13.7) Sensory Impairment: Normal =0, Diminished=1,Absent=2

	pain	touch	temperature	Position sense	vibration
Upper limb					
Lower limb					

13.8) neuropathic Pain (VAS Score): nil=0/mild=1/moderate=2/sever=3.



13.8) Pulse : ……./min

13.9) BP: ……..m m hg

13.10) Resp Rate: ……/min

13.11) JVP: normal/ Raised

13.12) other :if present,(specify)

14. Investigations:

14.1) CBC:

14.2) Urine R/E:

14.3) Serum creatinine: 14.4Serum Electrolytes:

14.5) LFT: a) SGPT: b) SGOT

c) PT: d) Serum Albumin:

14.6) OGTT a) FBS : b) 2 hr after 75 gm glucose:

14.7) HbA1C:

14.8) TSH

14.9) serum B12 assay:

14.10) CXR PA view

14.11) ECG

14.12) Echocardiography:

14.13) CSF Study:

14.14) NCS (Nerve conduction study):

15. Therapeutic Response:

Parameters	Assessment Before treatment (A 0) Date:	Assessment After 1 wk (A 1) Date:	Assessment After 6 wk (A 2) Date:	Assessment After 12 wk (A 3) Date:
A)Leg Swelling				
B)Muscle Power (MMRC grading) Upper Limb Lower Limb				
C)Deep Tendon Reflexes Upper Limb Lower Limb				
D)Squat Test				
E)Sensory impairment				
Pain				
touch				
position				
Vibration				
Tingling , Numbness				
Hyperaesthesia (VAS score)				
F) Muscle cramp (VAS score)				
H) Overall Neuropathy Limitation Scale (ONLS)	Arm Score…….. Leg Score…… Total:	Arm Score…….. Leg Score…… Total:	Arm Score…….. Leg Score…… Total:	Arm Score…….. Leg Score…… Total:

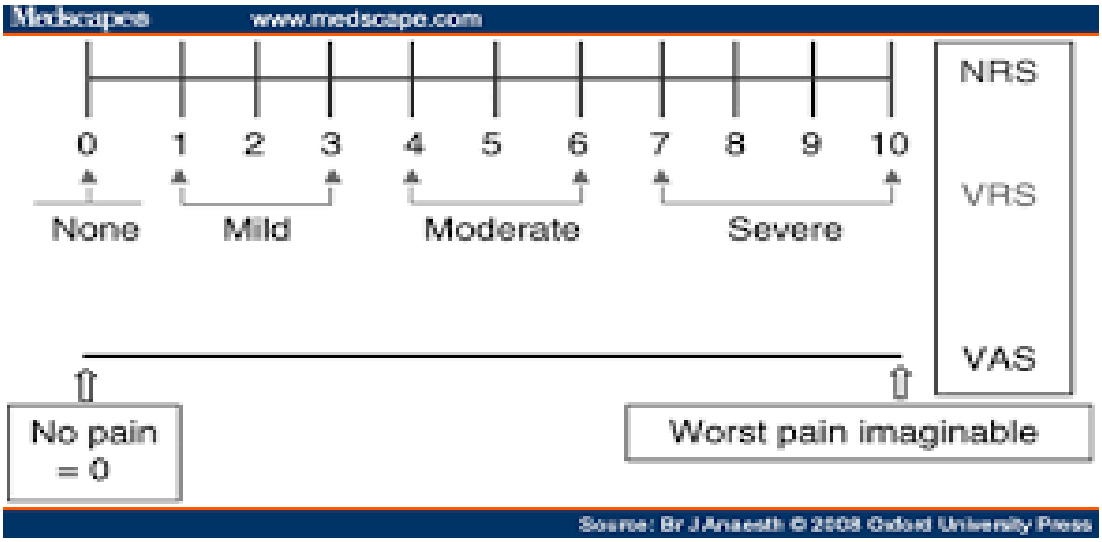
Medical Research Council (MRC) Scale for Muscle Power

0	**no muscle contraction visible**
1	**Flicker of contraction but no movement**
2	**Joint movement when effect of gravity eliminated**
3	**Movement against gravity but not against examiner's resistance**
4	**Movement against resistance but weaker than normal**
5	**Normal power**

Muscle tested for Power

Upper limb	Lower limb
Shoulder abduction	Hip flexion
Shoulder adduction	Hip extension
Elbow flexion	Knee flexion
Elbow extension	Knee extension
Supination	Foot dorsiflexion
Pronation	Foot planter flexion
Finger abduction & adduction	Great toe extension
Thumb opposition, abduction & adduction	Great toe flexion

Visual Analogue Scale (VAS) for pain



Neuropathic pain/Hyperaesthesia	VAS Score
Nil=0	0
Mild=1	1-3
Moderate=2	4-6
Severe=3	7-10

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question and observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE:

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? Yes/ No.

(if "no", please go to "legs" section)

Is the patient affected in their ability to: Not affected /Affected but not prevented/ Prevented

1. Wash and brush their hair
2. Turn a key in a lock
3. Use a knife and fork together (or spoon, if knife and fork not used)
4. Do or undo buttons or zips
5. Dress the upper part of their body excluding buttons or zips
6. If all these functions are prevented can the patient make purposeful movements with their bands or arms?

Arm Grade

0= Normal

1= Minor symptoms in one or both arms but not affecting any of the functions listed

2= Disability in one or both arms affecting but not preventing any of the functions listed

3= Disability in one or both arms preventing at least one but not all functions listed

4= Disability in both arms preventing all functions listed but purposeful movement still possible

5= Disability in both arms preventing all purposeful movements

Arm SCORE=

LEG SCALE

Does the patient have difficulty running or climbing stairs?
Does the patient have difficulty with walking?
Does their gait look abnormal?
How do they mobilise for about 10 metres (ie 33 feet)?

Without aid

With one stick or crutch or holding to someone's arm

With two sticks or crutches or one stick or crutch holding onto someone's arm or frame

With a wheelchair

If they use a wheelchair, can they stand and walk 1 metre with the help of one person?
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?

Does the patient use **ankle foot orthoses/braces?** (if yes,please circle) **right/left**

Leg grade

0= Walking/climbing stairs/running not affected

1= Walking/climbing stairs/running is affected, but gait does not look abnormal

2= Walks independently but gait looks abnormal

3= Requires unilateral support to walk 10 metres (stick, single crutch, one arm)

4= Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)

5= Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person

6= Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements

7= Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Is there any disorder, other than peripheral neuropathy, which affects the above functions: Yes / No
If **yes** please describe:

Leg SCORE=

TOTAL SCORE= (Arm SCORE) + (Leg SCORE)

Overall Neuropathy Limitation Scale = arm scale (range 0 to 5) + leg scale (range 0 to 7); range: 0 (no disability) to 12 (maximum disability).