

Clinical Presentation of Dry Beriberi Patients and Therapeutic Response to Thiamine Supplementation: A Hospital-Based Study in Bangladesh

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Abstract:

Background: Thiamine deficiency-related disorders are increasingly being reported in Bangladesh, as polished rice is the primary dietary constituent and the diet lacks balance in calorie, protein, and micronutrient content. Thiamine (vitamin B1) deficiency is often associated with sensory-motor neuropathy (dry beriberi) without Wernicke's encephalopathy and cardiac dysfunction. **Objectives:** The objective of our study was to observe the clinical presentation of suspected dry beriberi and to evaluate the therapeutic response to thiamine replacement. **Methods:** This study was a prospective, open-label, clinical trial (quasi-experimental study) carried out in the Neurology Ward of Chittagong Medical College Hospital from July 2018 to June 2019. Fifty-five (55) patients of suspected dry beriberi were recruited by convenience sampling. All patients were given 200mg IV Thiamine HCl daily for 1 week, then switched to oral Tablets. Thiamine 100mg twice daily for the remaining 11 weeks. They were evaluated clinically before treatment and followed up at the end of 1 week, 6 weeks and 12 weeks after treatment. The assessment was done by clinical parameters like leg swelling, muscle cramps, muscle power, squat test, sensory impairments, deep tendon reflexes and by Overall Neuropathy Limitations Scale (ONLS) Score. **Results:** There was a significant improvement in leg swelling ($p<0.001$), muscle cramp ($p<0.001$), muscle power ($p<0.001$), total score of Overall Neuropathy Limitation Scale (ONLS) ($p<0.001$) within 1 week of thiamine replacement. The treatment also successfully reduced individual components of sensory impairment (i.e. pain, touch, position, vibration) from baseline to 12 weeks ($p<0.001$). Only deep tendon reflexes did not return to normal in all patients within 12 weeks. Long time follow-up was needed for this. **Conclusion:** Thiamine replacement improved most clinical features of deficiency neuropathy (leg swelling, cramps, muscle power, sensory impairment, functional status). Clinicians should recognize varied presentations of neuritic beriberi and provide early supplementation.

Key words: Beriberi, Thiamine Supplementation, Dry Beriberi, Neuropathy

Introduction

Beriberi is caused by Thiamine (also called aneurin) deficiency which manifests itself by involvement of the nervous system, cardiovascular system and gastrointestinal tract.¹ The presence or absence of oedema is the basis of its old division into wet (cardiac) and dry (neuritic) beriberi. Dry beriberi is characterized by neuropathy, which can be associated with or without oedema, Wernicke's encephalopathy & Korsakoff psychosis. The term "Dry Beriberi" is a misnomer as it gives a false impression of the presence of oedema only in cardiac involvement. However, leg oedema can occur without cardiac involvement. It is newly termed "Thiamine deficiency with peripheral neuropathy".¹

Anyway, the overall prognosis for patients with thiamine deficiency is good as it is easily treatable and most signs and symptoms of the deficiency fully resolve with thiamine supplementation.¹ Beriberi is uncommon in developed countries due to the wide diversity of food and nutrition. In the developed world, it is only seen among alcoholics, patients receiving total parenteral nutrition, hemodialysis, bariatric surgery, cancer chemotherapy and those who are socially isolated, self-neglected, suffering from appetite loss and whose dietary intakes are high in carbohydrates but low in thiamine.² Beriberi remains a public health issue in Southeast Asia^{1,3-8} and Africa^{1,2,9} despite eradication elsewhere. The availability of milled rice as a cheap and popular food in urban areas and the lack of food diversity

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among poor people are important factors for the occurrence of thiamine deficiency in those areas.¹

In Bangladesh, there are no exact statistics regarding the prevalence of beriberi, although it is prevalent in the southern area of Chattogram division i.e. Satkania, Lohagara, Banshkhali, Anowara, Chandanaish Cox'sbazar, Moheshkhali, Kutubdia, Teknaf etc. It is an observation of our day-to-day clinical practice but why it is common in this region is a matter of interest. Recently, the number of homeless people in these areas has been increasing due to immigrants from neighbouring country Myanmar and they are at risk of nutritive problems. However, there is no documentation of the actual scenario in the literature review. In a poor country like Bangladesh, it is not always possible to confirm a diagnosis of beriberi with biochemical evidence as investigations are costly and not locally available. In our experience, most of them show positive responses to therapeutic trials of thiamine. It is indirect evidence of the existence of the disease. However, there is a paucity of any surveys or systematic studies on this issue. This situation has stimulated us to design this study to evaluate the clinical features of these patients and to assess their response to the thiamine trial systematically.

Materials and Methods

This quasi-experimental Clinical Trial was conducted in the Department of Neurology of Chittagong Medical College Hospital (CMCH) from July 2018 to June 2019. A total of 55 admitted adult (>18 years) patients of possible beriberi were included by a convenience sampling method based on the inclusion criteria. Patients with isolate cardiac/wet beriberi and with other known causes of peripheral neuropathy such as Diabetic, hereditary, Demyelinating (GBS, CIDP), metabolic (hepatic/renal impairment), history of intake of drugs (e.g. INH, Ethambutol, Phenytoin, Metronidazole, Dapsone etc.) and toxins exposure (As, OPC, Pb, Hg except alcohol) were excluded from study.

Operational Definitions:

Risk factors: 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 (within 1 month).

Possible/suspected dry beriberi: Any 1 of the Risk factors + at least 2 of the following signs:

1. Muscle weakness of upper and or lower limb (less than grade 5 power in MRC scale)
2. Positive sensory symptoms (burning, tingling or pain)
3. Objective sensory deficit (pain, touch, position, vibration sense)
4. Absent or reduced deep tendon reflexes
5. Positive squat test (unable to rise after squatting without help)
6. Leg swelling

Probable dry beriberi: Treatment with thiamine ameliorated the aforementioned symptoms.

Data collection Procedure: After selecting patients, detailed history, clinical examination and all other Information regarding sociodemographic and clinical profile were taken in a predesigned case record form. Relevant investigations (CBC, PBF, Serum creatinine, serum electrolytes, Liver function test, fasting & 2 hours after breakfast sugar, HbA1C, TSH, serum Vitamin B12, Chest X-ray, ECG, Echocardiography, CSF study and Nerve Conduction Study) were done to exclude differential diagnoses. Then therapeutic trial of Inj. Thiamine HCl was given IV for 1st week (200mg IV daily) then orally (tab. Thiamin HCl 100 mg bd) continued for 11 weeks. Patients were followed up after 1, 6 and 12 week to see the response based on some clinical parameters and Overall Neuropathy Limitations Scale (ONLS) score.

Statistical Analysis: Continuous data were reported as the means $\pm$ SD and interquartile range. Qualitative or categorical data were described as frequencies and percentages. At the final follow-up (12th Week), 35 patients out of 55 were available. The intention to treat analysis (ITT) analysis was used to determine the statistical significance. Missing values were replaced by the series means for this purpose. To determine whether pretreatment and post-treatment values were statistically significant or not, either Friedman's test or Cochran's Q test was used. The former test compares the quantitative variables and non-dichotomous qualitative variables and the latter test compares the dichotomous qualitative/categorical variables. Statistical significance was defined as $P < 0.05$ and the confidence interval was set at 95% level.

This study received approval from the Ethical Review Committee of Chittagong Medical College and the protocol was registered at ClinicalTrial.gov (NCT04977557).

Result

In our study, a total of 55 patients were included (16 males and 39 females) and out of 55, 35 subjects completed all 3 follow up (1 week, 6 weeks & 12 weeks after treatment). Nine (9) subjects dropped out at 6 weeks and 11 subjects dropped out at 12 weeks of follow-up and the dropout rate is higher in females (12 vs 8). The mean age of the study subjects was 31.1 ± 12.0 years (18-65 years). There was female predominance with a male-to-female ratio of 1:2.3.

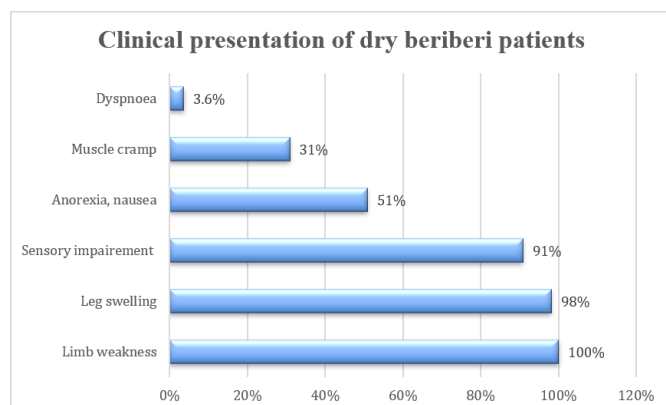


Figure 1: Clinical presentation of dry beriberi patients

Limb weakness was universal (100%), with leg swelling (98.2%) and sensory impairment (90.9%) common. Swelling occurred without cardiac involvement in 52 patients. Sensory symptoms were mostly tingling/burning (83.5%) rather than loss of sensation. Gastrointestinal features (anorexia, nausea) appeared in 50.9%, muscle cramps in 30.9%, and dyspnea in 2 patients (3.6%)—both showing normalized cardiac function after IV thiamine within 2 days.

Leg swelling was assessed by the pitting test (thumb pressure for 20 sec at the medial malleolus). Mild swelling resolved in 10 sec. Before treatment, 54 of 55 patients had swelling; all resolved by 6 weeks. Friedman's test with Dunn-

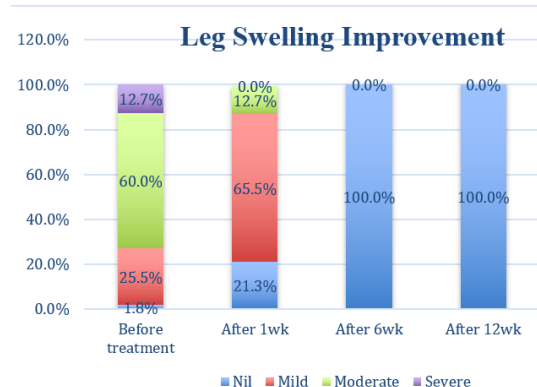


Figure 2: leg swelling improvement

The efficacy of thiamine was measured based on some clinical parameters which are described above.

Bonferroni post hoc analysis showed significant improvement between baseline and 1 week ($p < 0.001$) (Figure 2).

Muscle power was assessed using the MRC scale. Lower limb weakness was more severe than upper limb. Before treatment, 6 (10.9%), 40 (72.7%), and 9 (16.4%) patients had MRC scores of 4, 3, and 2, respectively. After 1 week of thiamine, 3 (5.5%) reached normal power (MRC 5), 43 (78.2%) improved to 4, and 9 (16.4%) to 3. At 12 weeks, 34 of 35 (97.1%) had normal lower limb power. Friedman's test showed significant improvement between baseline & 1 week, and 1 week & 6 weeks ($p < 0.001$) (Figure 3). For upper limbs, 18 (32.7%) had normal power at baseline, 35 (63.6%) scored 4, and 2 (3.6%) scored 3. After 1 week, 42 (76.4%) were normal and 13 (23.6%) scored 4. By 6 weeks, all patients had normal upper limb power ($p < 0.001$) (Figure 3).

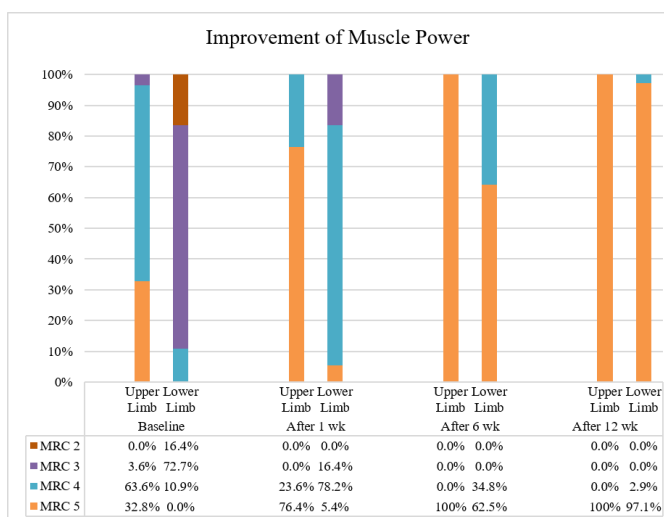


Figure 3: Improvement of muscle power

Squat test, assessing proximal lower limb strength, was positive in 54 (98.2%) patients at baseline. After thiamine therapy, gradual improvement was noted, with only 1 (2.9%) positive at 12 weeks (Figure 4). Cochran Q test with

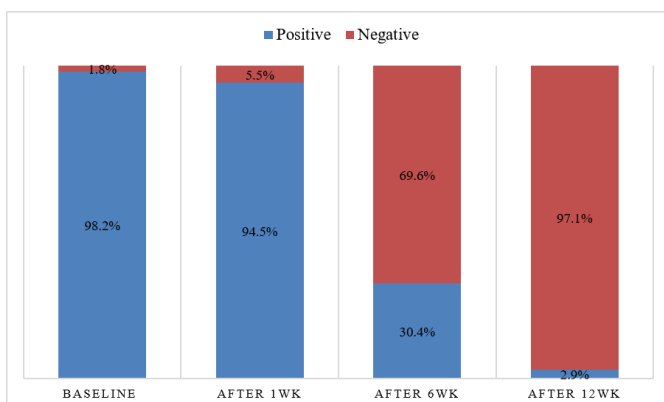


Figure 4: Squat test improvement

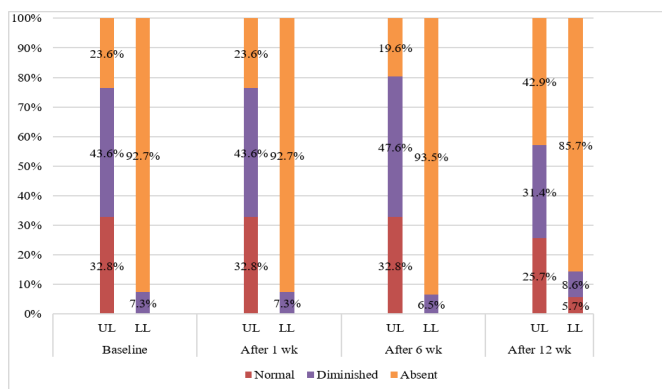


Figure 5: Deep Tendon Reflexes

pairwise comparison showed significant improvement between baseline and 6 weeks ($p < 0.001$).

Deep tendon reflexes (DTR) were absent in all lower limbs at baseline. After 12 weeks ($n=35$), 2 (5.7%) regained normal reflexes, 3 (8.6%) were diminished, and 30 (85.7%) remained absent. For upper limbs, 18 (32.7%) were normal at baseline; after 12 weeks, 15 (42.9%) were normal, 11

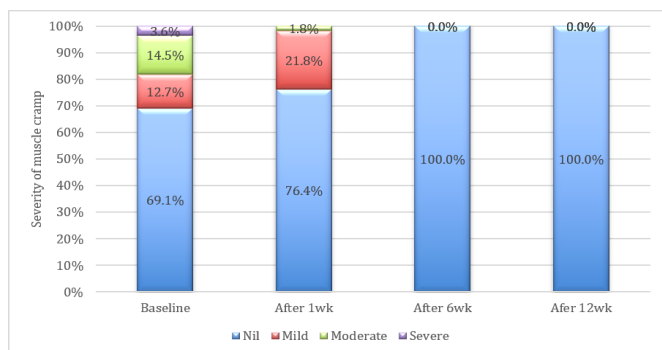


Figure 6: Muscle cramp improvement

(31.4%) diminished, and 9 (25.7%) absent (Figure 5). Friedman's test showed no significant changes over time in either limb.

Muscle cramps (VAS 1–10) were common at baseline. After 1 week of thiamine, cramps resolved in 42 (76.4%) patients; 12 (21.8%) had mild and 1 (1.8%) moderate symptoms. By 6 weeks, none had cramps. Friedman's test with Dunn-

Bonferroni post hoc showed significant improvement at 6 weeks ($p < 0.001$) (Figure 6).

Clinical improvement of sensory impairment was evaluated regarding pain, touch, position and vibration sensation. Before treatment 9 (16.4%) patients had diminished pain, touch, position and vibration sensation. After 12 weeks of thiamine treatment sensations return to normal in these patients ($P < 0.001$) (Table 1).

Overall Neuropathy Limitation Scale (ONLS): The ONLS (range 0–12; arm 0–5, leg 0–7) assesses functional disability, with higher scores indicating greater limitation. In our study, ONLS scores for arm, leg, and total decreased from baseline to 12 weeks post-treatment. At 12 weeks ($n=35$), 23 patients scored 0, 10 scored 1, and 2 scored 2. Arm function improved faster (within 6 weeks) than leg function, reflecting greater baseline disability in the lower limbs (Figure 7).

Discussion

A total of 55 patients were enrolled; 35 completed all three follow-ups. Nine dropped out at 6 weeks and 11 at 12 weeks, mainly due to perceived improvement or living in remote areas. Dropout was higher among females (12 vs. 8), reflecting dependence on male partners for travel. Most women were of reproductive age, with disease often precipitated by pregnancy or childbirth. Ahmed's retrospective study also noted thiamine-responsive neuropathy in peripartum women.⁴ Similarly, a Kashmir study found thiamine-deficiency neuropathy in 8 of 106 acute flaccid paralysis cases, 6 of whom were female.⁵ In Thailand's Karen displaced population, 6 of 18 pregnant women were biochemically thiamine-deficient at term.⁷

Most patients present with difficulty in raising from a sitting position followed by difficulty in walking, ultimately becoming completely bed-bound. Leg swelling was common. Weakness in the upper limb also occurs along with sensory impairment. Sensory impairment occurs in positive form (burning and tingling sensations) and also in negative form (numbness). Some complained of anorexia and nausea.

Table-1

Changes in pain, touch, position and vibration sensation over time

Sensory modalities	Baseline	After 1wk	After 6wk	After 12wk	P value*
Pain and touch					
Normal	46 (83.6%)	46 (83.6%)	41 (89.1%)	35 (100.0%)	0.001
Diminished	9 (16.4%)	9 (16.4%)	5 (10.9%)	0 (0%)	
Position and vibration					
Normal	46 (83.6%)	46 (83.6%)	40 (87.0%)	35 (100.0%)	0.000
Diminished	9 (16.4%)	9 (16.4%)	6 (13.0%)	0 (0%)	

*P values were derived from Cochran Q test

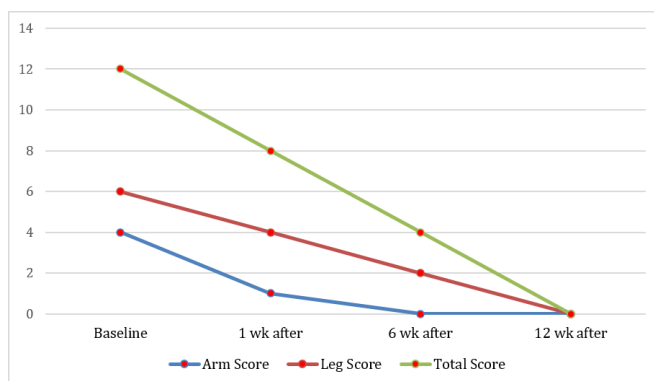


Figure 7: Effect of treatment on Overall Neuropathy Limitation Scale Score (ONLS)

Several other studies and case reports showed similarities in clinical presentations.³⁻¹⁰ Sometimes presentation is in the form of ascending flaccid neuropathy that closely mimics Guillain-Barre Syndrome¹¹⁻¹⁶ and critical illness neuropathy.¹⁷ In our study, most (87.27%) had objective evidence of mixed sensory-motor impairment. Only 12.72% had motor deficits without sensory complaints. No patient presented with sensory features alone. Koshy et al.⁶ conducted a study among peripartum women of suspected beriberi in India and found mixed sensory-motor features in 18 (75%), pure motor in 5 (21%) and pure sensory in only 1 (4%).

Weakness was more in limb muscles as these are frequently used. As lower limb involvement was more severe than upper limb, recovery was also late. All available study findings^{6,8-10} show subjective, objective and statistically significant improvement in muscle power after thiamine replacement.

Deep tendon reflexes did not return to normal as quickly as other improved clinical parameters. In a case report by Riahi et al.¹⁷, it returned to the lower limb after 6 months of treatment and even remained absent after 6 months of follow-up.¹⁶ In our 12-week study, it was absent in 30 patients, although they could walk independently.

Leg swelling, which was the most common presentation, disappeared within a few days of thiamine treatment and many patients noticed a swift diuresis after treatment which was consistent with all available study findings.^{2, 3, 5-7} In an Indian study involving peripartum women of Kashmir, leg swelling occurred without cardiac involvement in 24 (out of 27) cases.⁴ Improvement of muscle cramps was also similar in a study by Koike.¹³

Unlike leg swelling and muscle power, sensory impairment was the last to recover. According to some studies, sensory impairment may linger¹² but patterns of sensory impairments (stocking distribution) and sensory modalities (pain, touch, vibration, position sense, tingling/burning) were more or less similar to our study.^{11, 15-17} Improvement of positive sensory

symptoms (tingling/burning) recovery is better than improvement of negative sensory symptoms (pain, touch, position, vibration sense loss). None of our patients needed Pregabalin or any other drugs for neuropathic pain.

The overall Neuropathy Limitation Scale (ONLS) was used to see the functional limitations of respondents. Hakim et al.¹⁸ used the Total Symptoms Score (TSS) Scale and Quality of Life (QoL) score in evaluating patients with peripheral neuropathy after giving high doses of vitamins B1, B6 & B12. In that study, peripheral neuropathy was sensory predominant and TSS was suitable for evaluating sensory symptoms, but our patients were predominantly complaining of motor weakness and ONLS (overall neuropathy limitation scale) was suitable for our study.

An open trial with thiamine tetrahydrofurfuryl disulphide (TTFD) was carried out on 44 patients with nutritional polyneuropathy who were admitted to the Neurological Department, Dr. Soetomo Hospital, Surabaya, Indonesia.¹⁹ After 6 weeks of treatment, 34 patients showed improvement in their motor functions ($P < 0.01$) with a slight restoration of sensory function and reflexes ($P < 0.1$). TTFD was thought to be superior to Thiamine HCl as it achieves higher blood concentration with both oral and parenteral administration and the high level was maintained for longer. Its tissue affinity is much greater compared with that of ordinary thiamine and it is very little affected by thiaminase. We conducted the present study of 12-week duration by Thiamine HCl among 55 patients and the results were almost the same i.e. improvement of motor function ($p < 0.001$), deep tendon reflex UL ($p = 0.07$) LL ($p = 0.08$). Improvement of sensory impairment ($p < 0.001$) was better in our study as our study duration was 6 weeks longer than their study.

Limitations

Our study was limited by reliance on clinical criteria without laboratory confirmation, as in prior studies from India^{4,6} Taiwan,¹⁰ and Africa.²⁰⁻²¹ The erythrocyte transketolase test was unavailable due to cost. A control group was not feasible given ethical concerns, and dropout reduced longitudinal data. Despite these limitations, thiamine proved highly effective in reversing peripheral neuropathy when given early.

Conclusion

Thiamine replacement improved most clinical features of deficiency neuropathy (leg swelling, cramps, muscle power, sensory impairment, functional status). Clinicians should recognize varied presentations of neuritic beriberi and provide early supplementation.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

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