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

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Abstract

Background: Thiamine deficiency-related disorders are increasingly being reported in countries where polished rice is the main dietary constituent and diet is not balanced in calorie, protein and micronutrient contents. Thiamine deficiency is often associated with sensory-motor neuropathy (dry beriberi) without Wernicke’s encephalopathy and cardiac dysfunction.

Objectives: The objective of our study is to evaluate the efficacy of thiamine in patients with suspected dry beriberi.
Introduction

Beriberi is caused by Thiamin (also called aneurin) deficiency which manifests itself by involvements of the nervous system, cardiovascular system and also 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 and 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. But 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. Beriberi is uncommon in
developed countries due to food fortification and general improvement in living conditions. In the
developed world, it is seen among alcoholics, patients receiving total parenteral nutrition, hemodialysis,
bariatric surgery, cancer chemotherapy and in those who are socially isolated, self-neglected, suffering
from appetite loss and whose dietary intakes are high in carbohydrate but low in thiamine. Beriberi
remains a public health issue in south-east Asia and Africa despite eradication elsewhere. The great
outbreaks of thiamine deficiency in South-East Asia at the beginning of this century followed the large-
scale production of milled rice and its large-scale distribution. The availability of milled rice as a cheap
and popular food in urban areas was also a factor of importance for the occurrence of thiamine deficiency
in those areas. Thiamine deficiency was also recorded in refugee populations of Thailand at the
1995. [1]. In Bangladesh, there are no exact statistics regarding the prevalence of beriberi, although it
is thought to be prevalent in the southern area of the Chattogram division i.e. Satkania, Lohagara,
Banskhali, 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 this area is increasing due to immigrants from neighboring
county Myanmar and they are at risk of nutritional problems. But there is no documentation of the
actual scenario. In a poor country like Bangladesh, it is not always possible to document beriberi with
biochemical evidence. In our experience, most of them show a positive response to the therapeutic trial
of thiamine. It is indirect evidence of the existence of the disease. However, there is a paucity of any
survey or systemic study in this issue. This situation has stimulated us to design this study to evaluate
the clinical-epidemiological features of these patients and to assess their response to the thiamine trial
in a systematic way. In the future, a large-scale study is needed to highlight those common but neglected
problems and to the aware government of the situation as well as to formulate strategies to prevent
thiamine deficiency.

Materials and Methods

This Self-controlled Clinical Trial was conducted in the Department of Neurology and the Department of
Medicine of Chittagong Medical College Hospital (CMCH) from May 2018 to April 2019. A total of 55
patients of possible beriberi were included based on inclusion criteria. Patients with isolated 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 for
alcohol) are excluded from the 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, chronic, diuretics use, renal dialysis, total parenteral nutrition.

Possible/suspected neuritic (dry) beriberi: 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 neuritic (dry) beriberi: Above symptoms recovered after thiamine treatment.

Data Collection Procedure

After selection of subjects, detailed history, clinical examination and all other Information regarding sociodemographic and clinical factors of neuritic beriberi were taken in a prescribed case record form. Relevant investigations (CBC, PBF, Serum creatinine, serum electrolytes, Liver function test, fasting & 2 hours after breakfast sugar. HbA1C, TSH, Chest X-ray, ECG, Echocardiography, CSF study, Nerve Conduction Study were performed to exclude differential diagnoses. Then the therapeutic trial of Inj. Thiamine was given IV for 1st week (200mg IV daily) then orally (tab. Thiamin 100mg bd) for 12 weeks. Patients were followed up after 1, 6 and 12 weeks to see the response.

Statistical Analysis

Continuous data were reported as the means ± SD or median and interquartile range. Qualitative or categorical data were described as frequencies and proportions. At the final follow-up, 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 any of the difference between pre-treatment and post-treatment values were statistically significant or not, either Friedman’s test or Cochran’s Q test were used. The former test compares the quantitative variables and non-dichotomous qualitative variables and the later test compares the dichotomous qualitative/categorical variables. Statistical significance was defined as P < 0.05 and the confidence interval was set at 95% level.
Variables under study:

**Primary Outcome Variable:** Treatment response measured by Overall Neuropathy Limitation Scale (ONLS) score before and after treatment.

**Secondary Outcome Variables:** 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. This study has received approval from the Ethical Review Committee of Chittagong Medical College and all participants gave written informed consent.

**Results**

<table>
<thead>
<tr>
<th>Age, in years</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 years</td>
<td>4 (25.0%)</td>
<td>9 (23.1%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>21-30 years</td>
<td>4 (25.0%)</td>
<td>15 (38.5%)</td>
<td>19 (34.5%)</td>
</tr>
<tr>
<td>31-40 years</td>
<td>3 (18.5%)</td>
<td>13 (33.3%)</td>
<td>16 (29.1%)</td>
</tr>
<tr>
<td>≥41 years</td>
<td>5 (31.5%)</td>
<td>2 (5.1%)</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16 (29.1%)</strong></td>
<td><strong>39 (70.9%)</strong></td>
<td><strong>55 (100%)</strong></td>
</tr>
<tr>
<td><strong>Mean ±SD</strong></td>
<td>37.5±17.4</td>
<td>28.5±7.8</td>
<td>31.1±12.0</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>19-65</td>
<td>18-50</td>
<td>18-65</td>
</tr>
</tbody>
</table>

Table I: Age and sex distribution of the patients (n=55)
Figure 1: Efficacy of treatment in the reduction of leg swelling. Patients at baseline include n=55, at 1 week n=55, at 6 weeks n=46 and at 12 weeks n=35.

Analysis by Friedman’s test with Dunn-Bonferroni post hoc tests showed that there were significant differences between before treatment & 1 week after treatment (p<0.001), 1 week after & 6 weeks after treatment group (p<0.001).

Figure 2: Efficacy of treatment in the reduction of muscle cramp. Patients at baseline include n=55, at 1 week n=55, at 6 weeks n=46 and at 12 weeks n=35.

Analysis by Friedman’s test with Dunn-Bonferroni post hoc tests showed that there were significant differences between before treatment & 6 weeks after treatment (p=0.024) and between before treatment
& 12 week after treatment group (p=0.024).

Figure 3: Efficacy of treatment in improvement of muscle power of upper limb.

Analysis by Friedman’s test with Dunn-Bonferroni post hoc tests showed that there were significant differences between before treatment & 1 week after treatment (p<0.001), before treatment & 6 weeks after treatment group (p<0.001).

Figure 4: Efficacy of treatment in improvement of muscle power of lower limb.

Analysis by Friedman’s test with Dunn-Bonferroni post hoc tests showed that there were significant differences between before treatment & 1 week after treatment (p<0.001) and 1 week after & 6 weeks after treatment group (p<0.001).
Figure 5: Efficacy of treatment in improvement of deep tendon reflex of the upper limb.

Analysis by Friedman’s test showed that there were no significant differences between any time (p=0.07).

Figure 6: Efficacy of Treatment in the improvement of Deep Tendon Reflexes of Lower Limb.

Analysis by Friedman’s test showed that, there were no significant differences between any time (p=0.08).
Figure 7: Effect of treatment on Squat test. Patients at baseline include n=55, at 1 week n=55, at 6-week n=46 and 12 week n=35.

Analysis by Cochrain Q test with pairwise comparison showed there were significant differences between before treatment & 6 weeks after treatment group (p<0.001) and before treatment & 12 weeks after treatment group (p<0.001).

Table II: Changes in pain, touch, position and vibration sensation over time.

<table>
<thead>
<tr>
<th>Sensory Baseline modalities</th>
<th>After 1wk n=55</th>
<th>After 6wk n=46</th>
<th>After 12wk n=35</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain and touch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 46 (83.6%)</td>
<td>46 (83.6%)</td>
<td>41 (89.1%)</td>
<td>35 (100.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diminished 9 (16.4%)</td>
<td>9 (16.4%)</td>
<td>5 (10.9%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Position and vibration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 46 (83.6%)</td>
<td>46 (83.6%)</td>
<td>40 (87.0%)</td>
<td>35 (100.0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diminished 9 (16.4%)</td>
<td>9 (16.4%)</td>
<td>6 (13.0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

*P values were derived from Cochrain Q test
Table III: Effect of treatment on overall neuropathy limitation scale score (ONLS).

<table>
<thead>
<tr>
<th>Area</th>
<th>Median (IQR) of ONLS score</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment n=55</td>
<td>1 week after n=55</td>
</tr>
<tr>
<td>Arm</td>
<td>2 (1-3)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Leg</td>
<td>4 (4-4)</td>
<td>3 (3-3)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (5-7)</td>
<td>4 (3-5)</td>
</tr>
</tbody>
</table>

P values* were derived from Friedman’s test and are significant in all groups (p<0.001).

Discussion

Beriberi is still seen in Asian and African countries due to the large-scale consumption of thiamine-depleted polished rice [1]. Thiamine deficiency-related disorders are increasingly being reported from the southern area of Bangladesh but there is a lack of documentation on this. Specifically, a sensorimotor axonal neuropathy occasionally develops from thiamine deficiency and may occur even without associated Wernicke’s encephalopathy. Laboratory confirmation of beriberi in developing countries of the world including ours one is a real challenge. Administration of thiamine in cases of high clinical suspicion is appropriate as it is an effective, inexpensive, life savings and almost free of any serious adverse effect [1]. Our present study was an open-labeled, prospective, self-controlled clinical trial, carried out to see the efficacy of thiamine in patients with suspected dry (neuritic) beriberi. A total of 55 patients were included in the study (16 male, 39 female) and out of 55, 35 subjects completed all 3 follow up. Nine (9) subjects were dropped out at 6 weeks and 11 subjects dropped out at 12-week follow-up. Patients who had a subjective feeling of being improved after the initial therapy and those who live in the remote area did not come for follow-up. The dropout rate is more in females (12 vs 8) because of the dependence of male partners for long travel. In this study, the mean age of the subjects was 31.1±12.0 years (18-65 years). There was female predominance with a male to female ratio of 1:2.3. In males, the highest representation was from the age group ≥41 years in contrast to the 21-30 years age group in females. Females usually eat the leftover food after a male and may consume more thiamine depleted cereals to satisfy calorie needs, so achieve poorer thiamine: calorie ratio than men. It is evident that most females were in the reproductive age group and later it will be seen that disease was precipitated by pregnancy or delivery/childbirth. A hospital-based study done in Kashmir by Mohsin & Asimi [2], found that out of 106 patients with acute flaccid paralysis, eight patients had neuropathy because of thiamine deficiency, out of which 6 were females. Thus there is a suggestion that thiamine deficiency-related neuropathy may be common in females especially in the peripartum period in the Kashmiri community. In another study in the Gambia by Tang et al [3], showed attack rate was highest in a young male who is involved in heavy physical works. Their diet is carbohydrate predominant and
heavy physical exertion will raise thiamine requirements and depletes the body’s limited storage of thiamine. The efficacy of thiamine was measured based on some clinical parameters. These are leg swelling, muscle cramp, muscle power of involved limb, deep tendon reflexes, squat test, sensory symptoms and Overall Neuropathy Limitation Scale (ONLS) score. Improvements of those features were assessed over a definite time interval (after 1 week, 6 weeks and 12 weeks). Before treatment 54 patients, out of 55 had leg swelling. Among them, 14 (25.5%), 33 (60.0%), 7 (12.7%) had mild, moderate and severe leg swelling respectively. Those who had severe leg swelling 5 were pregnant (last trimester) and 2 had associated cardiac involvement. After 1 week of parenteral thiamine therapy, leg swelling was absent in 12 (21.3%) subjects, mild in 36 (65.5%) and moderate in 7 (12.7%) patients. After 6 weeks, there was no leg swelling among the available patients. These changes are statistically significant (p<0.001). Our findings are consistent with all available study findings [3, 4, 5, 6, 7], where leg swelling disappeared within a few days of Thiamine treatment and many patients in their study noticed a swift diuresis after treatment. At baseline 2 (3.6%) patients had severe muscle cramp and 8 (14.5%), 7 (12.7%), 38 (69.1%) had moderate, mild and no muscle cramp respectively. Severity was measured by VAS score (1 to 10). Those having score 1-3 is considered as mild, score 4-6 as moderate & score 7-10 as severe. After 1 week of parenteral thiamine therapy, muscle cramp disappeared in 42 (76.4%) patients. Only 1 (1.8%) patient had moderate and 12 (21.8%) had mild muscle cramp respectively. After 6 weeks of treatment, none of them had muscle cramps (P<0.024). A similar type of response is seen in a study by Koike et al. [8]. Muscle power was assessed by the MRC scale. At baseline 18 (32.7%) patients had normal muscle power (MRC 5) of the upper limb and 35 (63.6%), 2 (3.6%) MRC scale score 4 and 3 respectively. After 1 week of parenteral thiamine therapy muscle power improved and 42 (76.4%), patient’s scores became normal (MRC 5) and in 13 (23.6%) patient score became 4. After 6 weeks all patients had normal upper limb muscle power (p<0.001). Lower limb involvement was present in all patients. At baseline 6 (10.9%), 40 (72.7%) and 9 (16.4%) patients had MRC scale score 4, 3 and 2 respectively. After 1 week of thiamine therapy, 3 (5.5%) patients improved to MRC 5 score (normal power) and 43 (78.2%) and 9 (16.4%) patients’ scores increased to 4 and 3 respectively. After 12 weeks, among 35 available patients, 34 (97.1%) had normal lower limb muscle power (MRC 5). These changes were statistically significant (P<0.001). As lower limb involvement was more severe than upper limb, recovery was also late. All available study findings [3, 5, 6, 7] show subjective, objective and statistically significant improvement in muscle power. Finding are more or less similar in several case series by Krishna et al., [10] and Prakash et al. [9] in India. In some cases where the diagnosis is delayed foot drop did not improve after 6 months follow up. At the baseline of 18 (32.7%) patients had normal upper limb reflex and in 24 (43.6 %) and 13 (23.6%) patients reflexes were diminished and absent respectively. After 1 week of thiamine therapy, the deep tendon reflexes (DTR) pattern remains unchanged. After 12 weeks, among the available 35 patients, 15 (42.9%) patients had normal upper limb reflex and 11 (31.4 %) and 9 (25.7%) patients had diminished and absented DTR respectively. In the case of lower limb reflexes, before treatment, 4 (7.3 %) and 51 (92.7%) patients’ reflexes were diminished and absent deep tendon reflexes respectively. After 1 week of
thiamine therapy pattern remains the same. After 12 weeks among the available 35 patients, 2(5.7%) patients had normal lower limb reflex and 3(8.6 %) and 30(85.7%) patients had diminished and absented DTR respectively. DTRs do not return to normal as quickly as other improved clinical parameters. In a case report by Riahi et al. [11], it returns in the lower limb after 6 months of treatment, even remain absent after 6 months follow up [12]. In our 12 week study, it was absent in 30 patients though they can walk independently. The squat test is the ability to raise from a squatting position without support and is a function of the proximal muscle of the lower limb. Before treatment 54 (98.2%) patients had a positive Squat test. After treatment with thiamine the condition improved gradually and after 12week positive in only 1 (2.9%) patient (p<0.001). Our findings are similar to others [9, 10, 11]. Clinical improvement of sensory impairment was evaluated in terms of pain, touch, position and vibration sensation. Before treatment 9 (16.4%) patients had diminished pain, touch, position and vibration sensation. After 12wks of thiamine, treatment sensations return to normal in these patients. Tingling severity was also measured by VAS score. At baseline 3 (5.5%) patients had severe tingling and another 39 (70.9%) patients had moderate tingling and numbness. However, over time with treatment with thiamine the tingling/burning sensation reduced and after 12weeks all the available patients had no tingling and numbness. Unlike leg swelling and muscle power, sensory impairment is the last to recover. According to some studies, a sensory impairment may linger [13], but the pattern of sensory impairments (stocking distribution) and sensory modalities (Pain, touch, vibration, position sense, tingling/burning) are more or less similar to our study [11, 10, 9]. Improvement of positive sensory symptoms (tingling/burning) recovery is better than negative sensory symptoms (pain, touch, position, vibration sense loss). None of our patients needed Pregabalin for neuropathic pain. 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. After 6 weeks of treatment, 34 patients showed improvement of their motor functions (P<0.01) with the slight restoration of sensory function and reflexes (P<0.1). TTFD was thought to superior to Thiamine HCl as it achieves higher blood concentration with both oral and parenteral administration and the high level is maintained longer. Its tissue affinity is much greater compared with that of ordinary thiamine and it is very little affected by thiaminase. We conducted a present study of 12-week duration by Thiamine HCl among 55 patients and results are 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) is better in our study as our study duration is 6 weeks longer than their study. Overall Neuropathy Limitation Scale (ONLS) is used to see the functional limitations of respondents. The highest score is 12 (Leg score=7+ arm score=5) which indicates maximum disability and the lowest is 0 (normal). In our study ONLS score for arm, leg and total score reduced over time from baseline to 12 weeks after treatment. It is to be noted that, after 12 weeks among the available patients (n=35), 23 patients had a total score of 0, 10 patients had a score of 1 and only 2 patients had a score of 2. Arm score improved rapidly (within 6 weeks) than leg score as disability was more in the lower limb. Hakim et al (2018) used
the Total Symptoms Score (TSS) Scale and the Quality of Life (QoL) score in evaluating patients with peripheral neuropathy after giving high dose vitamin B1, B6 & B12. In that study, peripheral neuropathy is sensory predominant and TSS was suitable for evaluating sensory symptoms, but our patients are predominantly complaining of motor weakness and ONLS (overall neuropathy limitation scale) is suitable for our study. Our study is limited by small sample size, lack of laboratory confirmation of thiamine deficiency and use of clinical criteria alone to assess thiamine deficiency like several other studies done in India, Africa and Taiwan [5, 6, 14]. Erythrocyte transketolase activity- thiamine pyrophosphate effect test is a costly test and not done in our country, even not in our neighbouring country.

**Conclusion**

It can be concluded that most of the clinical features of thiamine deficiency peripheral neuropathy (Leg swelling, muscle cramp, muscle power, sensory impairment and functional status of patients) are improved from baseline after thiamine replacement. Only Deep Tendon reflexes of lower limbs were not returned to normal. Long-term follow-up is needed for this.

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**Conflict of interest:** There is no conflict of interest.

**References**


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