THIAMINE IN SEPSIS

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Introduction

• Properties of Thiamine
• Thiamine deficiency in critical illness
• Clinical situations associated with deficiency
• Current evidence on thiamine status and supplementation
• Evidence of Thiamine in septic shock
Thiamine (vitamin B$_1$)

- Present as various phosphorylated forms:
  - Thiamine pyrophosphate (TPP) is the most important and active form
- TPP is an essential cofactor for key enzymes involved in carbohydrate metabolism and energy production
Thiamine Pyrophosphate (TPP)

Pathway is blocked in Thiamine deficiency
Thiamine absorption & Elimination

• Max. absorption by the small intestines is 5 mg
• Body cannot produce thiamine and store up to 30 mg (80% as TPP)
  – 50% in skeletal muscles
  – heart, liver, kidney, nervous system including the brain
• Quick turnover rate, require continuous supplementation from food or other resources
• Elimination: by renal excretion
• The t½ is 9-18 days
Thiamine deficiency in critically ill

SHOULD BE SUSPECTED IN:

- Septic shock
- Burns
- Unexplained heart failure or lactic acidosis
- Neurological disorder in alcoholic patients
- Starvation
- Chronic malnutrition
- Long-term PN
- Bariatric surgery
Thiamine deficiency in critically ill

- Thiamine deficiency (TD) is prevalent among critically ill and associated with poor clinical outcome
- Is also prevalent in septic shock (20%-70%)
- Develop within 2 weeks of insufficient intake
  - Thiamine falls of rapidly from tissues except the brain
  - Urinary excretion drops to zero
  - Rapid recovery within hours following iv supplementation
Complications of Thiamine Def.

- Wet or dry beriberi
- Wet beriberi alters cardiac function mimicking S & S of heart failure
  - Shoshin beriberi, a life-threatening form with acute CV collapse, severe lactic acidosis and death if no treatment given
- Nervous system involvement
  - Neuropathic beriberi - affects lower limbs more than UL
  - can be permanent even following thiamine repletion
  - Wernicke-Korsakoff syndrome: confusion, ataxia and oculomotor abnormalities
Safety of thiamine administration

• Oral thiamine has a very low risk of adverse effects

• Parenteral is generally safe.
  – Rare cases of AEs from 100-300 mg and frequently at higher doses up to 500mg daily.

• Sporadic anaphylactic reactions have been reported
### Thiamine indications and posology

<table>
<thead>
<tr>
<th>Indication</th>
<th>Posology</th>
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<tr>
<td>RDA Enteral nutrition</td>
<td>1.0–1.2 mg/day; Minimum: 1.2 mg and a maximum dose of 10 mg/day. 2.2–2.9 mg per 1500 kcal daily feed</td>
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<tr>
<td>Parenteral nutrition (standard dose in multivitamin)</td>
<td>3.0–3.5 mg/day</td>
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<tr>
<td>Wernicke’s encephalopathy</td>
<td>Alcoholics: 200–500 mg i.v. three times daily</td>
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<td>Nonalcoholics: 100–200 mg/day i.v.</td>
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<td>Refeeding syndrome</td>
<td>On day 1, all patients should receive thiamine 200–300 mg i.v. at least 30 min before starting feeding and then 200–300 mg daily i.v. or orally until day 3 or 100 mg during nutrition (maintenance dose)</td>
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i.v., intravenous; RDA, recommended daily allowance.
Thiamine deficiency in critically ill patients with sepsis

Michael W. Donnino MD*, Erin Carney BA, Michael N. Cocchi MD, Ian Barbash MD,

- **Objective:** prevalence of absolute TD in critically ill patients with sepsis and association between thiamine levels and lactic acidosis
- **Design:** prospective observational study
- **Patients:** 30 patients with hypoperfusion or hypotension requiring vasopressor support. 30 control group was enrolled
- **Main results:** absolute TD defines as < 9nmol/L. No correlation between thiamine and lactic acidosis. In patients without liver dysfunction...
Thiamine and lactic acid

**Fig. 2** The statistically significant negative correlation ($P = .014$) between thiamine and lactic acid levels (log) in patients without liver injury pattern (ALT <240 IU/L).
Conclusion of the study

• Absolute TD is be prevalent in critically ill septic patients and appears to be underrecognized

• In the absence of liver dysfunction, lower thiamine levels are associated with higher lactic acid levels
Objective: To determine if IV thiamine would reduce lactate in patients with septic shock

Settings: Two US hospitals

Patients: Adult patients with SS and Lactate ≥3 mmol/L. Thiamine deficiency was defined as plasma level of ≤7 nmol/L

Interventions: Thiamine 200 mg vs Placebo twice daily for 7 days or until discharge

Primary outcomes: Lactate levels 24h after the first study dose
715 patients met inclusion criteria
(Sepsis, shock, and lactate > 3 mmol/L)

Excluded:
Liver dysfunction (n = 212)
Comfort measure only (n = 79)
Other reasons (n = 66)
Thiamine use (n = 56)
Metformin, linezolid, or anti-retroviral (n = 55)
Refused participation (n = 48)
No family present to consent (n = 27)
Cardiac arrest (n = 16)
Bowel or limb ischemia (n = 16)
Seizures within 3 hours (n = 14)
Enrolled but subsequently did not meet inclusion criteria (n = 13)
Enrolled in other interventional trial (n = 11)
Protected population (n = 4)
Non-English speaking (n = 4)
Previously enrolled (n = 2)

92 patients randomized

45 allocated to thiamine
- Received thiamine (n = 43)
- Did not receive thiamine (n = 2)
  - Did not meet inclusion criteria after randomization (n = 1)
  - Comfort care only before receiving study drug (n = 1)

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
43 patients analyzed

47 allocated to placebo
- Received placebo (n = 45)
- Did not receive placebo (n = 2)
  - Did not meet inclusion criteria after randomization (n = 1)
  - Bowel ischemia recognized after randomization (n = 1)

Lost to follow-up (n = 0)
Discontinued intervention (n = 1)
45 patients analyzed
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Thiamine (n = 43)</th>
<th>Placebo (n = 45)</th>
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<tbody>
<tr>
<td>Age – mean years (SD)</td>
<td>70 (14)</td>
<td>65 (17)</td>
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<tr>
<td>Sex – no. female (%)</td>
<td>17 (40)</td>
<td>19 (42)</td>
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<td>Race – no. white (%)</td>
<td>36 (84)</td>
<td>40 (89)</td>
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<tr>
<td>BMI* – kg/m² (SD)</td>
<td>29 (9)</td>
<td>29 (7)</td>
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<tr>
<th>Co-morbidities – No. (%)</th>
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<tr>
<td>Coronary artery disease</td>
<td>9 (21)</td>
<td>10 (22)</td>
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<tr>
<td>Congestive heart failure</td>
<td>10 (23)</td>
<td>12 (27)</td>
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<tr>
<td>Hypertension</td>
<td>24 (56)</td>
<td>22 (49)</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>10 (23)</td>
<td>13 (29)</td>
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<tr>
<td>Diabetes</td>
<td>19 (44)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>5 (12)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index* – median (quartiles)</td>
<td>2 (1, 3)</td>
<td>3 (1, 5)</td>
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<tr>
<th>Lactate values</th>
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<tr>
<td>Lactate – median mmol/L (quartiles)</td>
<td>4.1 (2.9, 5.0)</td>
<td>4.1 (3.1, 6.4)</td>
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<tr>
<td>Lactate &gt; 4 mmol/L – no. (%)</td>
<td>26 (60)</td>
<td>24 (53)</td>
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<th>Laboratory values at enrollment* – median (quartiles)</th>
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<tr>
<td>White blood count (x10³)</td>
<td>13.9 (8.7, 22.5)</td>
<td>13.1 (4.6, 19.3)</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.0 (8.9, 13.0)</td>
<td>10.4 (9.3, 12.5)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.8 (1.0, 2.6)</td>
<td>1.9 (1.4, 3.0)</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>145 (91, 191)</td>
<td>136 (116, 191)</td>
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<th>Mechanical ventilation and severity of illness</th>
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<tr>
<td>Mechanical ventilation at time of enrollment – no (%)</td>
<td>31 (74)</td>
<td>30 (67)</td>
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<tr>
<td>APACHE II score at enrollment – mean (SD)</td>
<td>25.7 (9.1)</td>
<td>26.5 (9.2)</td>
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<tr>
<td>SOFA score at enrollment – mean (SD)</td>
<td>10.1 (3.7)</td>
<td>10.2 (3.7)</td>
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Results

• No difference in primary outcome of lactate levels at 24h between the two groups

• No difference in secondary outcomes:
  – Time to shock reversal
  – Severity of illness and mortality

• (28) 35% of patients were TD at baseline
  – thiamine group had significant lower lactate at 24h (2.1 vs 3.1)
  – Significant decrease in mortality over time in those receiving thiamine in this subgroup
Lactate levels over time

**Complete group (n = 88)**

**Thiamine deficient group (n = 28)**
Kaplan Meier survival curves

Complete group (n = 88)

Thiamine --- Placebo

p = 0.85

Thiamine deficient group (n = 28)

Thiamine --- Placebo

p = 0.047
Conclusion of the study

• Thiamine did not improve lactate levels or other outcomes in the overall patients
• In those with baseline deficiency, thiamine group had significantly lower lactate levels at 24h and possible decrease in mortality over time
• Administration of thiamine is advantageous in septic shock patients with severe TD (≤7nmol/L)
• Further studies are needed, particularly targeting the deficient group
Limitations

- No information about management of SS patients
- Not shown whether IV thiamine resulted in significant increase in plasma thiamine at 24h
- Patients on epinephrine were not excluded (used in < 10%)
- Sample size for TD was small (n=28)
- Among 88 patients, only 8 (9%) patients were enrolled in the non-coordinating centre. Generalizability may be limited
- The dosage was based on historical dosages in other disease states.
- Dose finding trial for Effective dosages that resolved lactate elevation in pure TD were not performed
Lactic acidosis in septic shock

- Inadequacy between $\text{DO}_2$ delivery and $\text{O}_2$ demand by the tissues
  - Due to sepsis induced alterations in microcirculation
  - Mitochondrial dysfunction – activation of anaerobic metabolism and lactate production
- Non-hypoxic mechanisms
  - Accelerated aerobic glycolysis induced by sepsis-associated inflammation
  - Increased Na-K-ATPase activity through $\beta_2$ stimulation
  - Sepsis induced inhibition of pyruvate dehydrogenase complex
  - Impaired lactate clearance
  - Thiamine deficiency
Lactic acidosis in septic shock

- The source of lactic acidosis in SS is not usually identified.
- Measurement of plasma thiamine levels is not widely available,
  - take several days to perform.
  - Not helpful in decision making.
- Septic shock can have manifestations similar to fulminant Shoshin beriberi.
- Adverse effects of thiamine administration are uncommon at both low or high dose and the overall safety profile.
  - Septic shock patients should be given thiamine parenterally without waiting for the results of thiamine level.
Thiamine Supplementation

- ESPEN guidelines for PN in intensive care - 100-300 mg/day during first 3 days in the ICU for patients with suspected TD.
- Dosage up to 500 mg may be necessary for patients with septic shock
- Guidelines in UK - thiamine administered over 15-20 mins interval in a mixture of saline or dextrose to avoid AEs
Key messages

- Thiamine is an essential cofactor of key metabolic enzymes
- Thiamine deficiency is prevalent in critically ill patients, in septic shock up to 80%
- With low body stores and short t½, a deficiency is potentially life-threatening (e.g. Shoshin beriberi)
- Should be suspected in certain clinical scenarios
- Causes of increased lactate levels in septic shock are multifactorial and not easily identified by the bedside
- Parenteral Thiamine is generally safe.
- Thiamine repletion is a promising strategy in septic shock and should be considered.