The role of thiamine as a resuscitator in patients with nonalcoholic medical and CNS disorders

Mohamed Shehab-Eldin MD

ABSTRACT

Thiamine (vitamin B1), a water-soluble vitamin, is an essential factor in cellular metabolism and fundamental cofactor in important biochemical cycles. Thiamine deficiency is a well-known cause of neurological and cardiologic disorders, especially in patients with alcohol dependence. Recently, several researchers have studied the role of thiamine deficiency in critically ill patients and the link between thiamine supplementation and changes in lactate levels in septic shock patients. The role of thiamine in this group of patients is still unclear; however, thiamine supplementation does not cause toxic side effects or increase morbidity or mortality. In this review, we discuss the most common conditions associated with thiamine deficiency and the limited literature available on thiamine supplementation in critically ill patients.

Keywords: thiamine, sepsis, Wernicke encephalopathy, congestive heart failure

INTRODUCTION

Thiamine is a cofactor for pyruvate dehydrogenase (PDH), alpha ketoglutarate dehydrogenase (KGDH), and transketolase (TKT). As PDH cofactor, it is essential for the conversion of pyruvate into acetyl coenzyme A. In the absence thiamine, pyruvate is shifted into an anaerobic pathway and is converted into lactate.[1,2] Thiamine stores in the body are depleted after two weeks from the onset of a thiamine deficient diet; neurological symptoms of Wernicke encephalopathy occur after approximately four weeks. Other symptoms related to thiamine deficiency may develop after three months.[3]

Thiamine deficiency occurs secondary to increased metabolism in sepsis, decreased absorption in malnutrition, alcoholism, post-bariatric surgeries and hyperemesis, or increased carbohydrate intake with parenteral nutrition and intravenous dextrose solutions. With thiamine deficiency, several medical and neurological disorders can develop, including Wernicke encephalopathy and beriberi. Wernicke encephalopathy presents with ocular motor dysfunction, ataxia, and encephalopathy. Beriberi has two different types which are dry beriberi characterized by peripheral neuropathy which can occur concurrently with Wernicke encephalopathy and wet beriberi characterized by high output heart failure. Thiamine supplementation has definite benefits in alcoholic patients. However, it is controversial if patients with nonalcoholic neurological disorders benefit from thiamine supplementation, and it is still investigational whether thiamine has a role as a metabolic resuscitator in sepsis. Erythrocyte transketolase enzyme activity is the best biomarker for detection of thiamine deficiency.[4]

During healthy states, mitochondria produces more than 95% of the adenosine 5' triphosphate (ATP), initiate apoptosis and cell necrosis pathways,

Corresponding author: **Mohamed Shehab-Eldin**
Contact Information: Mohamed.Shehab-eldin@ttuhsc.edu
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regulate intracellular calcium, and sense oxygen levels. In acute states of sepsis or oxidative stress, there is a hypermetabolic state and transient mitochondrial damage or dysfunction develops secondary to the inhibition of the electron transport chain enzymes (Complex I and III) by nitric oxide, reactive oxygen species, and circulating hormones leading to genetic down regulation of mitochondrial protein expression and a decrease in mitochondrial activity. This mitochondrial dysfunction usually reverses in survivors; it is accelerated by the prolonged production of nitric oxide, despite its initial adverse effects on mitochondrial.[5] Thiamine has a protective effect on mitochondrial function; therefore, thiamine supplementation could improve disorders with mitochondrial dysfunction and reverse multiple organ dysfunction in sepsis. Thiamine deficiency can increase lactic acidosis during sepsis. The cause of thiamine deficiency in critically ill patients with sepsis is uncertain.

Role of thiamine deficiency and supplementation in systemic and neurological disorders

Sepsis

Septic shock is defined as severe sepsis with end organ dysfunction secondary to suspected or documented infection and hypotension not corrected by intravenous fluid resuscitation.[6] Sepsis induced hypotension is defined as a systolic blood pressure (SBP) less than 90 mmHg, or a mean arterial pressure (MAP) less than 70 mmHg, or a decrease in SBP by 40 mmHg or more than two standard deviations below the normal for age in the absence of other known causes for hypotension. During septic shock, lactic acidosis occurs secondary to hypoperfusion and organ dysfunction; in addition, the hypermetabolic state present during sepsis predisposes patients to decreased plasma levels of thiamine which lead to increases in lactate levels.[8] Pathophysiological events leading to lactic acidosis include inadequate oxygen delivery leading to a failure to meet the tissue oxygen demands during the hypermetabolic state associated with sepsis, impaired tissue oxygen extraction due to the microcirculatory dysfunction secondary to the endothelial inflammation, and impaired hepatic lactate clearance which is more severe in patients with hepatic disease.[9] Elevated lactate is associated with increases in acute hospital mortality when compared to lower lactate levels.[7,8] Considering this fact, researchers have hypothesized that thiamine supplementation during episodes of septic shock might decrease lactate levels and consequently reduce mortality. In critically ill patients without liver dysfunction, the frequency of thiamine deficiency has a significant negative correlation with lactic acidosis.[10]

Donnino et al have published the only randomized, double blind, placebo controlled study investigating the effect of intravenous thiamine supplementation on changes in lactate levels and mortality in patients with septic shock.[11] They hypothesized that intravenous thiamine supplementation in septic shock patients would demonstrate benefit in the treated cohort. The primary endpoint was lactate levels at 24 hours after the first thiamine dose. Eighty-eight patients were enrolled in the study and randomized in a 1:1 ratio. Forty-three patients were randomized into the intervention group which received 200 mg of thiamine for 7 days or until hospital discharge; 45 patients in the control group received placebo for the same duration. Baseline thiamine levels were measured in 79 patients, and 28 patients (35%) presented with baseline thiamine deficiency (15 patients in the intervention group, 13 in the control group). There was no difference in lactate levels 24 hours after the first dose of thiamine supplementation (P=0.40) or mortality between the two groups. In addition, there were no differences in the time to shock reversal or APACHE II scores at 24 hours or in the time to ICU discharge and hospital length of stay between the two groups. However, in the subset of patients who presented with thiamine deficiency, there was significant improvement in the lactate levels after 24 hours (P=0.03), but lactate levels did not normalize in this group.[11] This study's limitations include the small sample size which was underpowered to detect changes in mortality. There are no known toxic levels of thiamine, and even though the study did not find significant change in the clinical outcome in the septic shock patients, patients with septic shock who present with baseline thiamine deficiency

might benefit from thiamine supplementation during the acute phase of critical illness. Thiamine supplementation of 100-300 mg daily is safe.[2] Future well designed studies with a larger number of subjects should generate more information about the relationship between thiamine deficiency and /or supplementation and sepsis.

Central and peripheral nervous system disorders

Wernicke encephalopathy, a neurological disease exclusively secondary to thiamine deficiency, is characterized by a classic triad of ocular motor dysfunction with nystagmus and ophthalmoplegia, gait ataxia, and encephalopathy.[12] It is usually associated with alcoholism but rarely occurs with other conditions, such as post bariatric and other gastrointestinal surgeries, malignancy, AIDS, hyperemesis gravidarum, and malnutrition.[13] Wernicke-Korsakoff encephalopathy, when not related to alcohol, occurs almost twice as frequently in women as in men and has better survival rates in women.[13] Characteristic MRI brain findings on T2 FLAIR images include increased signal or hyper-intensity in the periventricular areas, mammillary bodies, thalami, and oculomotor and vestibular nuclei which correlates with the clinical presentation.[12] The absence of the radiological findings does not rule out this disease. Korsakoff psychosis is occasionally present with Wernicke and is characterized by an anamnestic confabulatory condition.[14]

A recent systematic review of 623 reported cases of non-alcoholic Wernicke-Korsakoff syndrome found that the most common cause was gastrointestinal disease or surgeries (34%), followed by hyperemesis gravidarum (18%), and dietary insufficiency or vomiting (17%). Outcomes of 611 patients showed death in 179 cases (29%), complete recovery in 129 cases (21%), moderate to severe cognitive impairment in 66 cases (11%), and improvement with residual symptoms, including cognitive impairment or complete recovery not reported, in 237 cases (39%).[13] There is no consensus about the effective thiamine dose for Wernicke encephalopathy; recommendations are for 500 mg of IV thiamine three times a day for two days followed by 500 mg daily for five days.[12] A lower dose of 200 mg has substantial benefit in non-alcoholics.[15] Dry beriberi syndrome is a progressive sensorimotor peripheral neuropathy secondary to thiamine deficiency that may occur independently or with Wernicke encephalopathy.[16]

The pathophysiology of the neurological dysfunction secondary to thiamine deficiency is unclear. During the last several years researchers have suggested that thiamine deficiency might alter astrocytic function by affecting astrocytic glutamate transporters and that the lactic acidosis accompanying thiamine deficiency causes changes in water channels and brain edema.[17]

Heart failure

Heart failure and thiamine deficiency have a reciprocal association. Low plasma thiamine levels can cause high output heart failure, a condition called wet beriberi syndrome.[2] Conversely, heart failure can cause thiamine deficiency possibly secondary to malnutrition and urinary loss of thiamine with diuretics use.[18] A recent meta-analysis evaluated the role of thiamine deficiency in patients with systolic heart failure.[19] This meta-analysis included nine studies that evaluated thiamine deficiency in heart failure patients versus non-heart failure patients; the total number of patients was 752 subjects (455 with heart failure and 297 controls). The prevalence of thiamine deficiency was higher in heart failure patients. In the systematic review, these authors considered the risk factors for thiamine deficiency in heart failure patients, and they concluded that the idea that loop diuretics caused thiamine deficiency was based on old and poor quality studies, and that more robust data from newer studies found no correlation between thiamine deficiency and the use of diuretics. This review indicated that thiamine supplementation resulted in a significant improvement in the quality of life in most patients. A few trials in the same review concluded that thiamine might improve the left ventricular ejection fraction and diuresis but does not decrease mortality in heart failure patients.[19]

Conclusions

In the last decade, there has been increasing interest in the role of thiamine supplementation in critically ill patients. The small number of studies available have demonstrated that thiamine is safe with no known side effects or toxic doses. There is no evidence to date that thiamine supplementation reduces mortality in critically ill patients with sepsis or congestive heart failure. However, some data suggest that selected patients with baseline deficiency might benefit from thiamine supplementation. Thiamine is safe, cheap, and available in most hospitals. Therefore, it might be reasonable to supplement thiamine in specific groups of patients with conditions not secondary to alcoholism during hospitalization. Well designed clinical trials are needed to provide robust data for the use of thiamine in critically ill patients with nonalcoholic conditions. In our hospital, we routinely administer thiamine to patients with alcohol withdrawal or dependence and Wernicke encephalopathy and perhaps should consider its use in other critically ill patients, especially if thiamine deficient.

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