Coronary artery bypass graft surgery depletes plasma thiamine levels

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Abstract

Objective: Thiamine is an essential component of cellular metabolism, and lack of this vitamin results in a potentially life-threatening biochemical lesion. The stress of surgery and critical disease depletes electrolytes, minerals, and essential biochemical substrates. We hypothesized that critical illness (represented by major surgery) would result in decreased thiamine levels over time.

Methods: We performed a prospective, observational study of serial thiamine levels of 15 patients who underwent non-emergent coronary artery bypass graft surgery. The primary endpoint was change in thiamine levels from before to immediately after surgery. Secondary endpoints included change in thiamine levels from presurgical to 6- and 24-h time points.

Results: Of the 15 study patients, 1 did not have a plasma thiamine measurement at time 0 because of laboratory error and could not be accounted for in paired comparisons over time. Plasma thiamine levels decreased significantly from before to after coronary artery bypass grafting ($P = 0.0004$). In addition, there was a statistically significant decrease in thiamine levels from before surgery to 24 h ($P = 0.003$).

Conclusion: Our data suggest that major surgery (as a surrogate for the stress of critical illness) depletes thiamine levels; further study is needed to determine whether routine replacement of thiamine in the critically ill is warranted. © 2010 Elsevier Inc. All rights reserved.

Keywords: Thiamine deficiency; Critical illness; Coronary artery bypass graft surgery

Introduction

Thiamine is an essential component of cellular metabolism with a key role in mitochondrial machinery. Specifically, thiamine is a cofactor for pyruvate dehydrogenase, the enzyme responsible for the conversion of pyruvate into acetyl-coenzyme A. A deficiency of this vitamin results in a potentially life-threatening biochemical lesion, because pyruvate cannot enter the citric acid cycle and is instead converted to lactic acid [1–3]. Thiamine deficiency may result in neurologic dysfunction (Wernicke’s encephalopathy), cardiac dysfunction (wet beriberi), peripheral polyneuropathy (dry beriberi), lactic acidosis, gastrointestinal beriberi, and death [1,3–10]. Moreover, lower levels of thiamine have been associated with increased mortality in the critically ill [11] and thiamine deficiency syndromes have been described in the intensive care setting [5,12–14].

Although electrolyte replacement therapy is routine for patients in a critical disease state or those undergoing the stress of surgery, little research or clinical consideration has been given to the potential loss of essential biochemical substrates or vitamins, specifically thiamine. As previously noted, the clinical consequences of thiamine deficiency may be severe and result in permanent neurologic dysfunction or death. We hypothesized that the stress of critical disease would result in decreased thiamine levels from increased metabolic demand. To test our hypothesis, we performed a prospective, observational study of serial thiamine levels of patients who underwent non-emergent coronary artery bypass grafting (CABG; major surgical stress).

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**Materials and methods**

**Design**

This prospective, observational study was conducted at an urban tertiary care center with 50,000 emergency department visits/year and intensive care units numbering a total of approximately 50 beds. This study was approved by the Beth Israel Deaconess Medical Center institutional review board and all patients provided informed written consent to participate.

**Inclusion criteria**

All outpatients older than 18 y who were undergoing elective CABG were eligible for inclusion. Data from all patients were included in the analysis. All patients were screened, consented, and enrolled before surgery.

**Exclusion criteria**

Exclusion criteria consisted of use of multivitamins, age younger than 18 y, or unwillingness to give consent.

**Procedures**

Plasma thiamine levels were measured before the operation, immediately after the operation, 6 h after the operation, and 24 h after the operation. The preoperation blood draw was performed in the preoperation area before the initiation of anesthesia. Blood was collected from patients by venipuncture or by a pre-existing arterial or venous catheter into two 5-mL tubes containing ethylenediaminetetra-acetic acid. Blood was centrifuged at 2000 g for 10 min after which 2 mL of this plasma was aliquoted into cryotubes and frozen. Blood was protected from light during the collection and freezing process. Frozen samples were sent to Quest Diagnostics (Chantilly, VA, USA). At Quest Diagnostics, plasma was deproteinized and then incubated with acid phosphatase to convert thiamine phosphate esters to free thiamine. The free thiamine was then oxidized to thiochrome by the addition of alkaline potassium ferricyanide. Depending on the age of the column and the temperature of the room, thiochrome retention time varied from 2.5 to 3.0 min. The mixture was injected to a Supelco (Bellefonte, PA, USA) high-performance liquid chromatographic column (7.5 cm × 4.6 mm, particle size 3 μm) connected to an high-performance liquid chromatographic system using a Hitachi (Pleasant, CA, USA) pump, autosampler, and fluorescent detector (excitation wavelength 365 nm, emission wavelength 440 nm). Seventy-five millimoles per liter of potassium phosphate at pH 7.5 with 25% methanol was used as the mobile phase for the high-performance liquid chromatographic system. The flow rate was set at 1.0 mL/min. Through this process, the thiochrome was then separated from other interfering substances and then measured fluorometrically. The amount of total thiamine in an unknown sample is proportional to the amount of thiochrome formed. Absolute thiamine deficiency was determined using a previously established standard laboratory reference range from Quest Diagnostics; specifically, absolute thiamine deficiency was defined as a level lower than or equal to 9 nmol/L.

**Statistical methods**

Baseline characteristics were reported with simple descriptive statistics. We used a paired t test to compare thiamine levels before and after CABG over time. The primary endpoint was the difference in thiamine levels before to immediately after the operation. P = 0.05 was used to determine statistical significance. Secondary endpoints included 6- and 24-h thiamine levels. To account for multiple measurements, we used Bonferroni’s correction factor to adjust the P value for significance such that P = 0.025 was considered statistically significant for time point differences between preoperative and 6- and 24-h postoperative thiamine levels.

**Results**

Twenty-five patients were screened, yielding a total of 15 study patients. The baseline characteristics of the study
patients are listed in Table 1. Of the 15 study patients, 1 did not have a plasma thiamine measurement at time 0 because of laboratory error and could not be accounted for in paired comparisons over time. Two patient samples may have had partial, premature thawing during transport; however, independent laboratory experts at Quest Diagnostics felt the results were unaffected. Moreover, all samples for each of these patients in question were equally affected (time 0 through time 24) and therefore all would have the same “relative” effect, if any did indeed occur. Thus, both patients were counted in the analysis.

Plasma thiamine levels over time are shown in Figure 1. For the primary endpoint, there was a statistically significant decrease in thiamine levels between baseline (before CABG) and serum thiamine levels after CABG (mean of differences 10.14 nmol/L, 95% confidence interval 5.6–14.7, \( P = 0.0004 \); Fig. 2). The secondary endpoint of preoperative to 24-h postoperative thiamine levels was also statistically significantly lower (mean of differences 8.5 nmol/L, 95% confidence interval 3.6–13.3, \( P = 0.003 \)); however, preoperative to 6-h postoperative levels were not significantly lower (mean of differences 5.8 nmol/L, 95% confidence interval −0.06 to 11.7, \( P = 0.052 \)).

**Discussion**

In patients undergoing CABG, thiamine levels decreased over time. Specifically, we found a statistically significant decrease in thiamine levels from before to immediately after CABG. In addition, there was a statistically significant decrease in thiamine levels from before surgery to 24 h after surgery. Thiamine is an essential component for multiple biochemical processes in the body, and depleted states may result in serious neurologic morbidity and even death [1]. The present investigation raises the possibility that the stress of critical illness (or, in this case, surgery) may deplete or decrease thiamine. The implications of this study are important because routine replacement of thiamine for critically ill patients is not widely performed particularly when patients are not known alcoholics (a population that traditionally receives thiamine supplementation).

Several small clinical investigations have evaluated thiamine levels in the critically ill but none within the CABG population using the methodology employed in the present investigation [11,15]. Thiamine deficiency in the critically ill has been described in two previous investigations using indirect measurements. Cruickshank et al. [11] examined thiamine deficiency in critically ill adults requiring parenteral nutrition. Using an indirect and functional measurement of thiamine deficiency (erythrocyte transketolase), they performed a retrospective analysis of 158 patients. Patients with higher body thiamine status as determined by erythrocyte transketolase had a lower mortality than those with lower levels of thiamine (72% versus 50%, \( P < 0.05 \)) [11]. However, this study was retrospective, used an indirect measurement of thiamine, and focused only on those who required parenteral nutritional support. In the pediatric intensive care unit, Seear et al. [15] found that 10 of 80 children (12.5%) were thiamine deficient based on erythrocyte transketolase levels. These investigations raised considerable concern for the prevalence of thiamine deficiency in the critically ill. In contrast to previous investigations in the critically ill, we measured baseline and “stressed” levels rather than levels only after entry into the critical care setting. Thus, we are able to judge the change in baseline levels after

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**Fig. 1.** Thiamine levels (mean ± SEM) over time.

**Fig. 2.** (Left) Group mean ± SE pre- and postsurgical thiamine levels. (Right) Paired comparison of thiamine levels before and after coronary artery bypass grafting were statistically significantly lower than preoperative thiamine levels (\( P = 0.0004 \)).
introduction of a significant stressor to the body. Second, we utilized direct rather than indirect measurements, thus mitigating the potential for confounding from other biochemical processes. A previous investigation evaluated thiamine levels before and after orthopedic surgery using the indirect thiamine assay and found that levels decreased over time [16]. Their findings are consistent with the present investigation. Moreover, the decrease of thiamine with increased cellular metabolism is consistent with laboratory models of thiamine activity. Specifically, McCourt et al. [17] found that, despite the catalytic role of thiamine, destruction occurs when thiamine is utilized in a reaction with pyruvate decarboxylase in a model derived from Escherichia coli. Thus, increased metabolic demand would logically increase usage and therefore lead to increased depletion consistent with the findings in the present report.

As stated, thiamine is an essential component of cellular metabolism without which neurologic dysfunction, cardiovascular dysfunction, or death may occur [1]. Thus, the implications of the present investigation are potentially of high importance for the routine management of critically ill patients. Thiamine is essential to a well-functioning mitochondrion; however, despite much attention to mitochondrial dysfunction in sepsis, few have considered the importance of this vitamin [18]. Like other electrolytes and biochemical products in the body, thiamine may need to be replaced in those with critical illness. Moreover, critical illness may actually require higher than normal levels similar to that of corticosteroids; however, this possibility remains unexplored.

That stated, the present study was not designed to determine the clinical significance of a decrease in thiamine over time but instead was designed to test the hypothesis of whether levels would change over time in the face of a significant stressor. We chose to evaluate patients with non-emergent CABG because this population is relatively healthy before surgery and then undergoes a tremendous stressor followed by a typically rapid recovery. Thus, the present study does not necessarily support widespread thiamine administration to the critically ill and postsurgical patient but instead illustrates that thiamine levels may decrease in the setting of physical stress and the consideration for replacement may need to be explored through future investigation.

Limitations

The sample size of the present study is small; however, there was adequate statistical power to conclude that thiamine levels decreased over time. This investigation was performed only on patients with CABG rather than other surgical conditions. Although we would expect similar findings in cohorts undergoing other surgical procedures or the stress of critical illness, this extrapolation is not definitive and may need to be tested. We chose to evaluate patients by using a direct assay for thiamine; whether the results of the study would differ if a functional assay of thiamine deficiency (i.e., erythrocyte transketolase) had been used remains unknown.

Conclusion

Thiamine levels are depleted over time in patients undergoing CABG. The depletion of thiamine raises concern that patients with critical illness or in the postoperative period may need thiamine replacement.

References