Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance[1–3]

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ABSTRACT

Background: Thiamine deficiency has been associated with poorer clinical outcomes. Early recognition of thiamine deficiency is difficult in critically ill patients because clinical signs are nonspecific.

Objective: We determined the prevalence of and identified risk factors associated with low blood thiamine concentrations upon admission of children to a pediatric intensive care unit and evaluated this condition as a predictor of clinical outcomes.

Design: A prospective cohort study was conducted in 202 children who had whole-blood thiamin concentrations assessed by HPLC upon admission to the intensive care unit. The following independent variables for thiamine deficiency were analyzed: age, sex, nutritional status, clinical severity scores upon admission (ie, the revised Pediatric Index of Mortality and Pediatric Logistic Organ Dysfunction score), systemic inflammatory response measured by C-reactive protein serum concentrations, severe sepsis or septic shock, heart failure, and cardiac surgery. The dependent variables in the outcome analyses were mortality, length of stay, and time on mechanical ventilation.

Results: Low blood thiamine concentrations upon admission were detected in 57 patients (28.2%) and were shown to be independently associated with C-reactive protein concentrations >20 mg/dL (odds ratio: 2.17; 95% CI: 1.13, 4.17; $P = 0.02$) but not with malnutrition. No significant association was shown between low blood thiamine concentrations upon admission and outcome variables.

Conclusions: The incidence of low blood thiamine concentrations upon admission was high. Of the risk factors examined, only the magnitude of the systemic inflammatory response showed an independent association with this event. The association between thiamine deficiency upon admission and prognosis requires further investigation. *Am J Clin Nutr* 2011;93:57–61.

INTRODUCTION

Thiamine is involved in several stages of intermediate metabolism that are important for producing energy. In the form of thiamine pyrophosphate, it acts as a cofactor in oxidative decarboxylation in 3 mitochondrial complexes (pyruvate, α-ketoglutarate, and α-keto-acids derived from branched-chain amino acids) and also as a cofactor of transketolase, which is a cytosolic enzyme involved in the pentose cycle and plays a role in maintaining cell redox status through the production of NADPH and glutathione. It is essential for converting pyruvate from glucose into acetyl coenzyme A for entry to the Krebs cycle where a thiamine deficit is followed by changes in intermediate metabolism that culminate in lactic acidosis (1).

Thiamin deficiency has been reported in diverse populations and patient groups. In a study in schoolchildren, thiamin deficiency was observed in 7.5% of the group, whereas >10% of the group presented borderline thiamine status (2). The reported prevalence of deficiency in adults upon emergency admission to hospital is 21% (3). It has also been associated with a poorer clinical outcome. In a retrospective study in critically ill adults in which laboratory biochemical values for thiamine and riboflavin were plotted against prognosis, patients who evolved to death had a higher incidence of low concentrations of these vitamins than did survivors. None of the patients studied presented any clinical signs of vitamin deficiency (4).

Although the clinical syndromes of deficiency classically manifest as beriberi, which progresses with cardiac insufficiency, peripheral neuropathy, and behavioral changes, and also as Wernicke-Korsakoff disease, other forms of manifestation have been described (5). Serious complications and death associated with thiamine deficiency in neonates who received long-term parenteral nutrition without vitamin supplementation have been reported. The cases occurred after a relatively short period of unsupplemented nutrition ranging from 10 to 30 d (6). More recently, 11 cases of severe encephalopathy were reported, 2 cases of which evolved to death, in infants fed exclusively on soy-milk formula that lacked thiamine (7–9).

To our knowledge, the prevalence of thiamine deficiency in critically ill children is not known, and only one pediatric study on this issue, which involved a group of predominantly well-nourished children, has been conducted (10).

Clinical signs and dietary history lack sensitivity and specificity for diagnosing deficits, and guidelines suggest empirical administration of the same doses recommended in healthy individuals to critically ill children. If potential deficiencies are indeed being underdiagnosed, then it is important to identify the

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prevalence, risk factors, and patient groups that may benefit from supplementation. On the basis of the hypothesis that thiamine deficiency is frequent in critical ill children, this study sought to determine the prevalence and identify factors associated with low blood thiamine concentrations upon admission of children to an intensive care unit and to evaluate the role of this event as a predictor of clinical outcomes.

SUBJECTS AND METHODS

This was a prospective cohort study. Children admitted to the pediatric intensive care unit (PICU) of a university-teaching hospital with 7 beds, (The Hospital of São Paulo of the Federal University of São Paulo) classified as level 1A (11), between January 2006 and January 2008 were eligible for inclusion in the study. Premature newborns were excluded as were patients who received vitamin supplements that contained thiamine, patients with encephalic death, and patients who were expected to stay <24 h. The study was previously approved by the Research Ethics Committee of the university. Thiamine deficiency was defined as a blood vitamin concentration below the lower limit for normality. The following independent variables for thiamine deficiency were analyzed: age, sex, nutritional status upon admission, clinical severity scores upon admission [revised Pediatric Index of Mortality (PIM 2) and Pediatric Logistic Organ Dysfunction (PELOD) score], magnitude of inflammatory response [measured by serum C-reactive protein (CRP) concentrations], severe sepsis or septic shock, congestive heart failure (CHF), cardiogenic shock and cardiac surgery. These diagnoses were elected as risk factors because of their association with severe inflammatory activity (sepsis and cardiac surgery) or because B_1 hypovitaminosis can cause or contribute to cardiac dysfunction (cardiogenic shock or CHF).

For classification of nutritional state, anthropometric indexes of weight and height were compared against the World Health Organization 2006 growth standards (12). Patients were considered malnourished when they presented a z score of the anthropometric index less than –2; a cutoff of 3 z scores below the reference median was taken to indicate severe malnutrition. The weight-for-age index was used as the anthropometric index for children <2 y of age, the weight for height index was used for children between 2 and 10 y of age, and body mass index was used for children >10 y old. Besides these conditions, all children with chronic diseases who presented a z score of height-for-age less than −2 were considered malnourished. Calculations of z scores were performed by the World Health Organization Anthroplus software (version 1.0.2; World Health Organization, Geneva, Switzerland).

Clinical severity upon admission was assessed according to the PIM 2 (13). The PELOD score was used to assess multiple organ dysfunction severity on the day of admission. The PELOD score was calculated by summing up the points for each verified organ dysfunction (14). Systemic inflammatory response syndrome, severe sepsis, and septic shock were defined according to pediatric consensus terminology (15).

Thiamine deficiency was considered an independent variable for the outcome analyses, whereas dependent variables included in-PICU mortality, length of PICU stay, and length of mechanical ventilation.

Laboratory analyses

An HPLC-based method (Immundiagnostik AG, Bensheim, Germany) (16) was used to measure whole-blood thiamin concentrations with the reference range for normality as 16–48 ng/mL. Deficiency was defined as a blood thiamine concentration <16 ng/mL. To ensure quality control, the method was validated in normal subjects and adult intensive care unit (ICU) patients. Serum CRP concentrations were assessed by turbidimetry (17) on the basis of a reference value of normality ≤0.6 mg/dL for acute-phase inflammatory diseases. Blood samples were collected ≤48 h of admission.

Statistical analyses

The chi-square test was used to analyze categorical variables, whereas the Mann-Whitney test was used to verify differences in thiamine concentrations between infants and older children. Differences were considered significant when the 95% CI of the odds ratio (OR) did not include the value of 1 for each independent variable. Categorical variables that presented a significant association with the outcome in the bivariate analysis with $P < 0.2$ were included in the logistic regression model. Data were expressed as medians and interquartile ranges. A P value of 0.05 was set for rejection of the null hypothesis. The Intercooled Stata 8.0 software (StataCorp LP, College Station, TX) was used for statistical analyses.

RESULTS

A total of 202 patients were included in the analysis during the study period. The main characteristics of patients studied are summarized in **Table 1**.

TABLE 1
Demographic and clinical characteristics of patients upon admission to the pediatric intensive care unit (n = 202)[1]

Variable	Values
Age (y)	1.7 (0.5–7)[2]
Sex [n (%)]	
M	108 (53.5)
F	94 (46.5)
PIM 2 (% predicted mortality)	2. 5 (1.1–6.5)
$PELODd_1$	2. 00 (1–11)
Length of hospital stay (d)	5. 00 (3–11)
Time on lung mechanical ventilation (d)	3 (1–8)
Diagnostic groups [n (%)]	
Severe sepsis or septic shock	28 (13.9)
Cardiogenic shock or CHF	19 (9.4)
Cardiac surgery	38 (18.8)
Respiratory	40 (19.8)
Neurologic	33 (16.3)
Renal failure	17 (8.4)
Others	27 (13.4)
Nutritional status [n (%)]	
Well nourished	109 (53.96)
Malnourished	93 (46.04)
Severely malnourished	52 (25.74)

[1] PIM 2, revised Pediatric Index of Mortality; $PELODd_1$, Pediatric Logistic Organ Dysfunction score on the day of admission; CHF, congestive heart failure.

[2] Median; interquartile range in parentheses (all such values).

TABLE 2
Bivariate analysis for assessment of exposure variables for low blood thiamine concentrations upon admission[1]

Variable	Frequency of low thiamine concentrations	Odds ratio (95% CI)	*P*
Age <1 y	18/76	0.69 (0.36, 1.32)	0.26
Male sex	32/108	1.16 (0.62, 2.15)	0.63
PIM 2 >6.5% (75th percentile)	14/50	0.98 (0.48, 2.00)	0.96
$PELOD_1$ >1 (75th percentile)	13/39	1.35 (0.63, 2.86)	0.42
Diagnosis			
Cardiogenic shock or CHF	4/19	0.65 (0.20, 2.06)	0.33
Severe sepsis or septic shock	6/28	0.65 (0.25, 1.71)	0.38
Cardiac surgery	11/38	1.04 (0.47, 2.27)	0.91
Malnutrition	30/93	1.52 (0.82, 2.82)	0.18
CRP concentration >20 mg/dL	38/109	2.23 (1.16, 4.26)	0.01

[1] PIM 2, revised Pediatric Index of Mortality; $PELOD_1$, Pediatric Logistic Organ Dysfunction score on the day of admission; CHF, congestive heart failure; CRP, C-reactive protein. Pearson's chi-square test was used for analysis.

The median (interquartile range) blood thiamin concentration upon admission was 25.8 ng/mL (15.2–31.6 ng/mL). No significant difference in thiamin concentrations was shown between infants and older children; the median (interquartile range) thiamin concentrations in these groups were 25.85 ng/mL (17.7–33.25 ng/mL) and 25.8 ng/mL (14.92–30.47 ng/mL), respectively. Thiamine deficiency upon admission occurred in 57 (28.2%) patients. Clinical signs of thiamine deficiency were not identified in the patients, with the exception of one child who presented psychiatric disturbances and had been diagnosed with Wernicke syndrome, which was confirmed by brain magnetic nuclear resonance, low blood concentrations of thiamine, and good response to intravenous thiamine.

The following exposure variables for deficiency upon admission with $P \leq 0.20$ in the bivariate analysis were included in the logistic regression model: CRP concentrations >20 mg/dL and malnutrition (**Table 2**). In the multivariate analysis, malnutrition showed no independent association with thiamine deficiency upon admission, whereas a CRP concentration >20 mg/dL was an independent risk factor for deficiency (**Table 3**). Patients with CRP concentrations >20 mg/dL had a 2.3-fold higher risk of thiamine deficiency upon admission than other patients (OR: 2.29; 95% CI: 1.19, 4.40).

The overall mortality observed in the PICU for the study group was 6.4% (13 of 202 patients). In the bivariate analysis, no significant association was shown between thiamine deficiency upon admission and clinical outcome variables, and severe sepsis or septic shock showed a tendency of association with mortality

TABLE 3
Logistic regression model for assessment of variables associated with low blood thiamine concentrations upon admission[1]

Variable	Incidence	Odds ratio (95% CI)	*P*
Protein-energy malnutrition	41/126	1.16 (0.77, 2.71)	0.24
CRP concentration >20 mg/dL	39/108	2.17 (1.13, 4.17)	0.02

[1] CRP, C-reactive protein.

TABLE 4
Logistic regression model for assessment of variables associated with mortality in the pediatric intensive care unit

Mortality	Odds ratio (95% CI)	*P*
Low blood thiamine concentration	0.28 (0.03, 2.36)	0.24
Severe sepsis or septic shock	1.43 (0.28, 7.26)	0.66
Thiamine deficiency plus severe sepsis or septic shock	17.39 (0.80, 74.69)	0.06

($P = 0.08$). Thiamine deficiency combined with severe sepsis or septic shock was shown to be associated with higher mortality (OR: 8.40; 95% CI: 1.38, 51.0; $P = 0.02$), although this association did not prove to be independent in the logistic regression analysis (**Table 4**).

DISCUSSION

The most important findings of this study were the high prevalence of low blood thiamine concentrations upon admission in the patients studied and the association between this deficiency and high concentrations of CRP.

The B-1 family of vitamins comprises thiamine together with its phosphate esters: thiamine monophosphate, thiamine diphosphate (TDP), and thiamine triphosphate. Thiamine concentrations are transiently decreased in plasma as part of the systemic inflammatory response; therefore, plasma assays have poor sensitivity and specificity, especially in critically ill patients (18). The majority of thiamin content in total blood (>90%) is observed in red blood cells in the form of TDP. Because the rate of TDP depletion in erythrocytes is similar to thiamin depletion in other organs, thiamin concentrations in erythrocytes provide a good indication of body stores of thiamine (19). Accordingly, there is strong correlation between TDP concentrations in erythrocytes and concentrations in total blood (20). On the basis of this premise, the current study used the thiamine concentration in whole blood as an indicator of body stores of the vitamin. Direct measurements of thiamine stores were used in preference to functional assays (ie, a transketolase activation assay or transketolase activity assay) because the latter assays can be influenced by factors other than vitamin deficiency. Such confounding factors include relatively poor interassay precision, a lack of standardization of functional methods, and sample instability after storage because of rapid transketolase enzyme inactivation (20, 21).

The prevalence of low blood thiamine concentrations was higher than that shown in the other available pediatric study, which was conducted in a heterogeneous group of patients and regarded the severity of disease and thiamine supplementation; 12.5% of 80 predominantly well-nourished children admitted to the ICU were thiamine deficient (10). Because infants have a high metabolic rate and faster rate of growth, they could be expected to represent a high-risk age group for deficiency. After assessment of whole-blood thiamine by the modified thiochrome method, authors suggested that the reference values for blood thiamine concentrations should be adjusted for age because concentrations tended to be significantly higher in the first months of life (22). Because these values were not validated by the HPLC method, the reference values recommended by the laboratory were

adopted in our investigation. Consequently, the prevalence of low blood thiamine concentrations may have been underestimated in our patients who belonged to this lower age group. Nevertheless, no significant difference in thiamine concentrations was shown between infants and older children.

Malnutrition is associated with an increased risk of B-complex vitamin deficiency (23). However, in the current study, no significant association between low blood thiamine concentrations and malnutrition was shown. Possible explanations could be the increased intestinal reabsorption of thiamine that takes place under deficient conditions and is associated with the depletion of body stores of the vitamin (24) and because anthropometric data are known to be poor predictors of early vitamin deficiency. Notwithstanding, the presence of malnutrition should be taken into account when identifying patients at risk of deficiency.

Although adult patients with CHF and who use furosemide are considered a high risk group for thiamin deficiency (25), studies in children have not corroborated this finding (26). Likewise, patients admitted with cardiac dysfunction in the current study did not represent a high-risk group for thiamine deficiency.

Sepsis was shown not to be associated with low blood thiamine concentrations upon admission. CRP proved more effective than the use of clinical variables in the current analysis. Patients with CRP concentrations$>$ 20 mg/dL had a 2-fold higher risk of low blood thiamine concentrations upon admission than other patients. High CRP values reflected a greater magnitude of inflammatory activity and therefore of intermediate metabolism, a situation that leads to a higher consumption of the cofactors that act in carbohydrate metabolism, including thiamin (1). Alternatively, thiamine deficiency may trigger inflammation. Experimental models have shown an association between deficiency of this vitamin and expression of gene-related inflammation, whereby this association is believed to play an important role in the cause of the neuronal dysfunction and demise that occurs in Wernicke encephalopathy (27). In a recent study carried out in 70 critically ill adult patients, no correlation between red cell thiamine concentrations and CRP was shown (28). The main reasons that hamper comparisons with our study are the sample size and because thiamine status was assessed by a microbiological thiamine assay, which is a method with the main drawback of the potential for organism inhibition by therapeutic antibiotic concentrations in blood.

Low blood thiamine concentrations alone, or combined with other risk factors, showed no significant association with clinical outcomes. However, the analyses suggested a tendency toward this association in patients with severe sepsis or septic shock. The fact that mortality in children admitted to the ICU is lower than in adults precludes the use of death as a clinical outcome variable. The effect of an intervention or exposure variable on mortality in pediatric patients may be better studied in specific population groups with a higher overall mortality, such as in individuals with sepsis or acute respiratory distress syndrome.

Septic patients experience hypoxia and are susceptible to reperfusion injury. Because thiamin is a coenzyme in metabolizing glucose, it is a crucial component for ATP regeneration. Thiamine deficiency in hypoxia-ischemic or reperfusion states can be conducive to and exacerbate cell dysfunction or death (29). The protective effect of thiamine against hypoxia-induced cell death and reperfusion injury has been shown in experimental studies in which the cell death rate decreased substantially after addition of thiamine (30, 31). Thiamine also plays a fundamental role in glutathione regeneration and may indirectly act as an antioxidant (32, 33).

The low number of septic patients in the current study may partly explain the lack of confirmation of the hypothesis that the absence of the protective effects of thiamine could contribute to a higher mortality in thiamine-deficient septic patients. Therefore, a limitation in the analyses of clinical outcomes was the small sample size in subgroups, which prevented the clear assessment of the effects of vitamin deficiency as a risk factor. In view of the clinical importance of this issue, further studies that investigate this hypothesis in larger samples of septic patients are warranted. Another limitation of the current study was the absence of a validated pediatric reference range by an HPLC method. Because several HPLC-based methods for the measurement of TDP in whole blood have been reported in the literature, it is suggested that each laboratory defines its own normality range (20). Although we cannot say with any certainty whether values below the normal range indicate a state of thiamine deficiency, the lower reference value provided by the laboratory represented a cutoff point that was approximately the first quartile of the study sample distribution. Therefore, the expression *low thiamine blood concentrations* is more appropriate than the term *thiamine deficiency.*

In conclusion, the magnitude of inflammatory response represented a risk factor for low blood thiamin concentration upon admission to the PICU. This knowledge can enable a potential state of deficiency to be detected early upon admission and, thereby, allow timely treatment and prevention of deficiency-related complications. This study can form a basis upon which to devise future studies during an ICU stay, to evaluate the prognostic significance of this event in septic patients, and to clearly define specific functional abnormalities related to low blood vitamin concentrations.

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