Thiamine as a Renal Protective Agent in Septic Shock

A Secondary Analysis of a Randomized, Double-Blind, Placebo-controlled Trial

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Abstract

Rationale: Acute kidney injury (AKI) is common in patients with sepsis and has been associated with high mortality rates. The provision of thiamine to patients with sepsis may reduce the incidence and severity of sepsis-related AKI and thereby prevent renal failure requiring renal replacement therapy (RRT).

Objectives: To test the hypothesis that thiamine supplementation mitigates kidney injury in septic shock.

Methods: This was a secondary analysis of a single-center, randomized, double-blind trial comparing thiamine to placebo in patients with septic shock. Renal function, need for RRT, timing of hemodialysis catheter placement, and timing of RRT initiation were abstracted. The baseline creatinine and worst creatinine values between 3 and 24 hours, 24 and 48 hours, and 48 and 72 hours were likewise abstracted.

Results: There were 70 patients eligible for analysis after excluding 10 patients in whom hemodialysis was initiated before study drug administration. Baseline serum creatinine in the thiamine group was 1.2 mg/dl (interquartile range, 0.8–2.5) as compared with 1.8 mg/dl (interquartile range, 1.3–2.7) in the placebo group ($P = 0.3$). After initiation of the study drug, more patients in the placebo group than in the thiamine group were started on RRT (eight [21%] vs. one [3%]; $P = 0.04$). In the repeated measures analysis adjusting for the baseline creatinine level, the worst creatinine levels were higher in the placebo group than in the thiamine group ($P = 0.05$).

Conclusions: In this *post hoc* analysis of a randomized controlled trial, patients with septic shock randomized to receive thiamine had lower serum creatinine levels and a lower rate of progression to RRT than patients randomized to placebo. These findings should be considered hypothesis generating and can be used as a foundation for further, prospective investigation in this area.

Keywords: sepsis; renal insufficiency; multiple organ failure; beriberi; mitochondria

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Acute kidney injury (AKI) is common in patients with sepsis and has been associated with higher mortality rates (1, 2). The pathophysiological understanding of kidney injury in sepsis has traditionally focused on renal hypoperfusion from cytokine-mediated vasodilation, ultimately resulting in acute tubular necrosis and renal failure (3, 4). However, recent studies have challenged this paradigm, illustrating that sepsis-associated kidney injury often occurs in the face of adequate perfusion (5, 6). These findings suggest that alternative pathophysiologic mechanisms, such as redistribution of renal blood flow, venous

congestion, microcirculatory failure, cytopathic hypoxia, and the release of proinflammatory cytokines, may have a role in developing AKI (7). Recent studies also suggest that G1 cell cycle arrest of renal tubular epithelial cells might play an important part in the development of sepsis-induced AKI (8, 9). Unfortunately, there are no presently approved pharmacologic agents for either the prevention or treatment of sepsis-related AKI.

One potentially modifiable etiology of renal injury in sepsis may be mitochondrial dysfunction in which cells are unable to extract and/or use oxygen for aerobic metabolism even if adequate oxygen delivery is present (10). Beriberi secondary to thiamine deficiency is a well-known cause of vasodilatory shock and inadequate cellular oxygen extraction in the face of high cardiac output/adequate perfusion, which has previously been associated with renal failure (11–14).

Thiamine is a key factor in aerobic metabolism, working as a cofactor for pyruvate dehydrogenase (15, 16). In the absence of thiamine, pyruvate is unable to enter the Krebs cycle, and pyruvate is converted to lactate rather than acetyl-coenzyme A. Thiamine deficiency, therefore, causes a shift in metabolism to the anaerobic pathway, resulting in elevated serum lactate levels, cellular apoptosis, organ injury (including renal failure), and possibly death (8, 17, 18). As thiamine deficiency appears to be relatively common in critical illness, and has been previously associated with lactic acidosis and hypotension, thiamine supplementation has emerged as an attractive pharmacologic means of enhancing mitochondrial function in sepsis (19, 20). To date, however, the effect of thiamine supplementation on the prevention or treatment of sepsis-related AKI has not been studied.

In the present study, we hypothesized that the provision of thiamine to patients with septic shock may reduce the incidence and severity of sepsis-related AKI and thereby prevent renal failure requiring renal replacement therapy. To test this hypothesis, we performed a *post hoc* analysis of a prospective randomized trial of thiamine in septic shock.

Methods

Trial Design, Study Population, and Intervention

This was a secondary analysis of a randomized, double-blind trial comparing the administration of intravenous thiamine to placebo in patients with septic shock (20). Adult patients presenting with sepsis (defined as the presence of two or more systemic inflammatory response syndrome criteria with documented or suspected infection), lactate greater than 3 mmol/L, and hypotension (systolic pressure $<$ 90 mm Hg) after a minimum of a 2-L fluid bolus followed by vasopressor dependence were included in the study. Patients were randomized in a 1:1 ratio to thiamine (200 mg in 50 ml 5% dextrose) or placebo (50 ml 5% dextrose) twice daily for 7 days. Thiamine levels were measured in plasma via liquid chromatography/tandem mass spectrometry by Quest Diagnostics (Nichols Institute, Chantilly, VA). 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 less than or equal to 7 nmol/L. Study protocols, exclusion criteria, and main results have been previously published by our group (20).

Clinical records of patients enrolled in the trial at the coordinating site were reviewed. Premorbid medical comorbidities were abstracted by a physician blinded to study group assignment through review of the past medical history section of the clinical records. Renal function, need for renal replacement therapy (RRT), indication for RRT, and timing of RRT initiation were abstracted. Patients who received study drug (thiamine or placebo) after the decision to initiate RRT was made or who received RRT before the current admission were excluded from the analysis. The baseline creatinine and worst creatinine values between 3 and 24 hours, 24 and 48 hours, and 48 and 72 hours were likewise abstracted.

Statistical Analysis

Descriptive data are provided according to treatment group; continuous data as means with SDs or medians with interquartile range (IQR), depending on the distribution of the data. Categorical data are presented as counts and percentages. Between-group comparisons were made with Fisher exact test for categorical data and *t* tests or Wilcoxon rank sum tests for continuous data, as appropriate. Repeated measures of worst creatinine levels were compared between the groups using repeated measures analysis. Creatinine levels were log-transformed before this analysis. We included time, group (placebo vs. thiamine), and the baseline creatinine level in the model. An unstructured variance-covariance structure was used. If a patient received RRT, creatinine levels were imputed by carrying forward the last known value before initiation of RRT. No imputation was performed for patients who died. All hypothesis tests were two-sided, with a significance level of $P < 0.05$. Statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

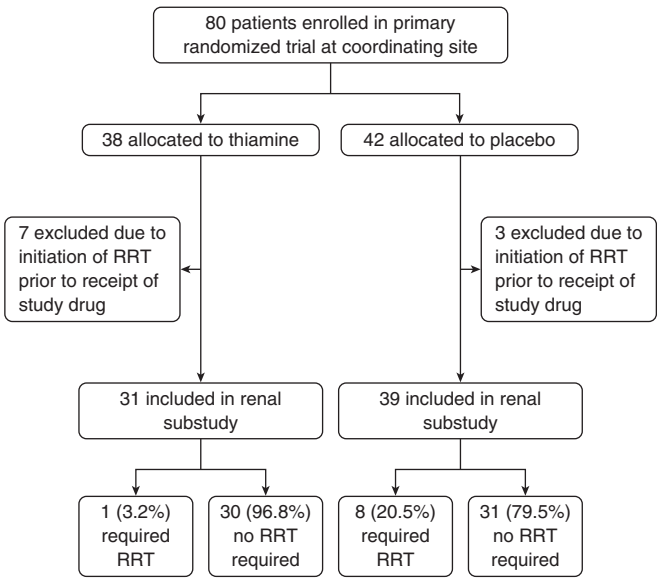

Figure 1. Flow diagram detailing study population and primary outcome. RRT = renal replacement therapy.

Results

Eighty patients were enrolled in the original trial at the coordinating center. RRT was initiated before study drug administration in 10 patients (7 [18%] in the thiamine group and 3 [7%] in the placebo group, $P = 0.18$), leaving 70 patients for the primary analysis in the current study (Figure 1). Baseline patient characteristics are presented in Table 1.

After initiation of the study drug, more patients in the placebo group than in the thiamine group were started on RRT (eight [21%] vs. one [3%]; $P = 0.04$). The primary indication for RRT initiation was acidosis in six cases (66.7%), including in the one patient who had been randomized to the thiamine group. Of the remaining cases, the indication for RRT initiation was volume overload in one case (11.1%) and uremia in two cases (22.2%). Median time from study drug administration to RRT initiation was 26 hours (interquartile range, 11–78 hr). In the repeated measures analysis adjusting for the baseline creatinine level, the worst creatinine levels were higher in the placebo group than in the thiamine group ($P = 0.05$; Figure 2).

Of the 70 patients included in this study, in-hospital mortality was 37.1%, with rates of 32.2% and 41.0% in the thiamine and placebo groups, respectively ($P = 0.45$). Among the patients who received RRT, 6 (66.7%) expired as compared with 20 (32.8%) who did not receive RRT ($P = 0.05$). In an exploratory analysis of thiamine-deficient patients, 2 of 11 patients in the placebo group ultimately required RRT, as compared with 0 of 12 patients in the thiamine group ($P = 0.22$).

Table 1. Selected baseline characteristics of the study patients

Characteristic	Thiamine ($n = 31$)	Placebo ($n = 39$)	P Value
Demographics			
Age, yr, mean (SD)	68 (16)	66 (17)	0.6
Sex, female, n (%)	13 (42)	17 (44)	0.9
Race, white, n (%)	26 (84)	36 (92)	0.04*
BMI,† kg/m^2, mean (SD)	30 (10)	29 (7)	0.8
Comorbidities, n (%)			
Coronary artery disease	4 (13)	9 (23)	0.3
Congestive heart failure	5 (16)	11 (28)	0.2
Hypertension	15 (48)	18 (46)	0.9
Chronic pulmonary disease	8 (26)	12 (31)	0.7
Diabetes	11 (35)	6 (15)	0.05*
Insulin dependent	3 (10)	5 (13)	
Renal disease	3 (10)	6 (15)	0.5
Charlson Comorbidity Index, median (IQR)	2 (1–3)	2 (1–5)	0.3
Laboratory values at enrollment, median (IQR)			
White blood count, $\times 10^3$‡	13.9 (7.3–21.8)	13.1 (4.6–19.5)	0.6
Hemoglobin, g/dl‡	10.3 (8.5–13.3)	10.7 (9.3–12.6)	0.5
Creatinine, mg/dl	1.2 (0.8–2.5)	1.8 (1.3–2.7)	0.3
GFR, ml/min/1.7 m^2	62 (29.6–91.8)	42.1 (27.3–54.7)	0.3
KDIGO stage 4 or 5, n (%)	8 (25.8)	12 (30.8)	0.7
Glucose, mg/dl§	146 (95–190)	146 (128–193)	0.5
Lactate, mmol/L	4.1 (2.6–4.6)	3.8 (3.0–5.5)	0.9
Potassium, mEq/L§	4.3 (3.8–4.8)	4.4 (3.9–4.9)	0.7
Bicarbonate, mEq/L§	22 (17–23.0)	19 (17–22)	0.5
Blood urea nitrogen, mg/dl†	33.5 (20.5–55.5)	31 (21–47.5)	0.9
Thiamine deficient, n (%)	12 (38.7)	11 (28.2)	0.4
Mechanical ventilation and severity of illness			
Mechanical ventilation at time of enrollment, n (%)	23 (74)	25 (64)	0.4
APACHE II score at enrollment, mean (SD)	24.9 (9.3)	25.7 (9.5)	0.7
SOFA score at enrollment, mean (SD)	9.3 (3.3)	9.9 (3.7)	0.4

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; GFR = glomerular filtration rate: Modification of Diet in Renal Disease formula; IQR = interquartile range; KDIGO = Kidney Disease: Improving Global Outcomes Stage; SOFA = Sequential Organ Failure Assessment score.
*Statistically significant.
†Data missing on three patients.
‡Data missing on nine patients.
§Data missing on six patients.

Discussion

In this *post hoc* analysis of a prospective randomized trial, we found that patients receiving thiamine had less progression to renal failure requiring renal replacement therapy than those in the placebo arm. In addition, we found that patients receiving thiamine had lower creatinine levels than patients in the placebo group.

Sepsis-associated kidney injury is common. Recent data from the Protocolized Care for Early Septic Shock (ProCESS) trial suggest that the incidence of AKI in patients with septic shock is in excess of 30% (1). Although the definition of AKI differs somewhat between studies, other investigators have demonstrated even higher incidence rates (21). Furthermore, the development of renal injury has been shown to have a strong association with poor outcome (1, 2).

Although the previously accepted pathophysiologic explanation for organ failure in sepsis was predicated largely on cytokine-mediated vasodilation and related hypoperfusion, other mechanisms of organ injury in sepsis have recently been proposed (22, 23). In a systematic review of kidney histopathology in septic kidney injury, a minority (22%) had microscopic features of acute tubular necrosis (24). A similar pattern was found in animal models of sepsis-related AKI, where just 184 of 1,059 animals (17.4%) were found to have acute tubular necrosis. Of those animals who suffered acute tubular necrosis, all had low cardiac output and decreased renal blood flow. In contrast, the more common histopathological pattern appeared to be one of tubular cell apoptosis (25).

In the present study, we identified a higher rate of kidney injury and need for renal replacement therapy in patients with septic shock who did not receive thiamine than in those who received thiamine. These data, in combination with

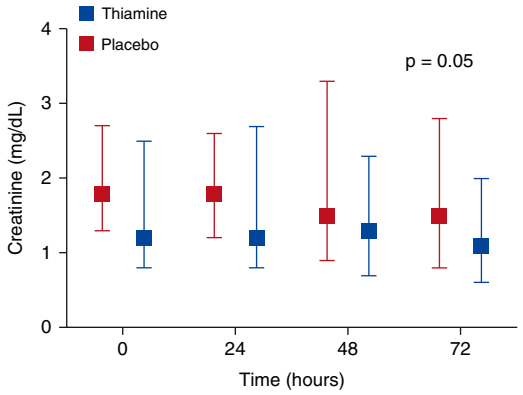

Figure 2. Creatinine levels over time according to treatment group.

the literature reviewed above, suggest that mechanisms other than renal hypoperfusion may have contributed to the increased rate of kidney injury and renal failure in the placebo arm of this randomized trial. As thiamine deficiency has been tied to increased apoptosis in neurons (26), vascular endothelium (27), retinal pericytes (27), and cardiac myocytes (28, 29), we hypothesize that thiamine supplementation may have prevented apoptosis-related cell death in renal tubular cells.

Our study has a number of limitations. Foremost, given the *post hoc* nature of our study design and small sample size (which increases the statistical fragility and chances of type I error), the results should be considered hypothesis-generating and not evidence of a causal link between thiamine deficiency and sepsis-related kidney injury. In addition, there was an imbalance in baseline renal function and medical comorbidities between patients in the control and intervention arms (Table 1), which may limit internal validity. Although these differences did not reach statistical significance, the lack of significance may be due to the small number of patients in the study and resultant low power to detect a difference. Finally, in patients who received RRT, post-RRT creatinine levels were imputed by carrying forward the last known value before initiation of RRT. Although this should bias toward the null (true renal function had likely worsened and not remained constant leading up to RRT initiation), these missing data are a limitation of our *post hoc* design.

Conclusions

In this *post hoc* analysis of a randomized controlled trial, patients with septic shock randomized to receive intravenous thiamine had lower serum creatinine levels and a lower rate of progression to RRT than patients randomized to placebo treatment. Given an emerging understanding of sepsis-related AKI that focuses increasingly on cytopathic hypoxia and tubular apoptosis, our results raise the possibility of a renal-protective role of thiamine supplementation. Due to the small sample size of this study and *post hoc* design, the results presented here should be considered hypothesis generating and future, prospective animal and human studies are needed to better clarify the role of thiamine in sepsis-related renal dysfunction. ■

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