Commentary

Thiamine as a metabolic resuscitator in septic shock: one size does not fit all

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Thiamine is an essential component of cellular metabolism, and the lack of this vitamin can result in life-threatening biochemical damage (1). Specifically, thiamine is a cofactor in oxidative decarboxylation in three mitochondrial complexes (pyruvate, α-ketoglutarate and α-keto acids). In addition, this vitamin is also a cofactor of transketolase, an enzyme involved in the tricarboxylic acid cycle (2,3). Therefore, thiamine deficiency can lead to the onset of anaerobic metabolism, associated with severe lactic acidosis. The classical clinical presentations of thiamine deficiency are Wernicke-Korsakoff encephalopathy; peripheral neuropathy, muscle weakness and anorexia (dry beriberi), high-output heart failure (wet beriberi), and beriberi associated with shock (Shoshin beriberi) (4-6).

Thiamine deficiency has been reported in diverse populations and patient groups. Several studies have found thiamine deficiency to be prevalent in different critically ill conditions, such as prolonged parenteral nutrition, dialysis, post bariatric surgery, and burns. Importantly, thiamine deficiency is also prevalent in patients with septic shock, with rates ranging from 20% to 70%, depending on study design (7-10). In addition, elevated concentrations of serum lactate, metabolic acidosis, and hypotension occur in both thiamine deficiency and septic shock. It would be logical to hypothesize that thiamine deficiency might occur in the pathophysiology of septic shock. Therefore, thiamine could represent an attractive therapeutic target in patients with septic shock.

Recently, Donnino *et al.* (9) evaluated the effects of thiamine as a metabolic resuscitator in septic shock. It was a two-center, randomized, double-blind trial comparing thiamine supplementation versus placebo in adult patients (n=88) with septic shock. Inclusion criteria were age ≥18 years, sepsis (presence of two or more SIRS criteria with documented or suspected infection), lactate >3 mmol/L, and hypotension after ≥2 L fluid bolus followed by vasopressor-dependence. The primary outcome was lactate level 24 hours after the first study medication dose. Secondary outcomes included lactate levels at 6 and 12 hours as well as lactate change at 24 hours, time to shock reversal, APACHE II score at 24 hours, SOFA score at 24 hours, intensive care unit and hospital length of stay, and in-hospital mortality.

The results showed that there was no difference in primary and secondary outcomes. Interestingly, 35% of the patients were thiamine deficient at baseline. In this subgroup, those in the thiamine treatment group had statistically lower lactate levels at 24 hours [2.1 (1.4–2.5) mmol/L *vs.* 3.1 (1.9–8.3) mmol/L, P=0.03], and a decrease in mortality [2 (13%) *vs.* 6 (46%), P=0.047].

The results of the study by Donnino *et al.* (9) suggest relevant clinical implications. Firstly, thiamine deficiency is a common condition in critically ill patients. Secondly, the most recommended biomarker for detecting thiamine deficiency is erythrocyte transketolase activity. However, this is an expensive test that is not available in most services (6). Thirdly, the signs of thiamine deficiency and other disorders such as septic shock are similar. Finally, early thiamine supplementation in doses from 100 to 300 mg/day for 3 days was safe for critical patients and at low risk of adverse events (11). Therefore, at this time, we suggest that it might be interesting to broadly supplement thiamine for all patients with septic shock.

However, some limitations should be taken into account

when interpreting the results of the study by Donnino *et al.* (9). The reduction of lactate levels and mortality was only found in subgroup analysis, comprising a small sample size (n=28). Importantly, for the 24 hours' time point, lactate levels were imputed based on a pre-defined plan in patients who died before this time point. So, if the patient died before the 6 hours' time point (five patients) a 20% increase from baseline was imputed, if patients died between the 6 and 12 hours' time point (one patient) a 15% increase from baseline was imputed, if patients died between the 12 and 24 hours' time point (six patients) a 10% increase from baseline was imputed. This method of dealing with the missing data could have biased their result. In addition, proper treatment of shock resuscitation alone could be responsible for the decrease in lactate levels and acidosis improvement. Another important issue is that, considering only patients with baseline thiamine deficiency, APACHE II and SOFA scores are unknown, as well as other potential confounders between patients who did and did not receive thiamine. Furthermore, there is no information whether there were any patients with thiamine deficiency whose lactate values were imputed as previously described. There is also no data on potential differences in the treatment of patients, with baseline thiamine deficiency. Therefore, important differences regarding demographic and clinical characteristics could have interfered with the results.

In conclusion, we believe that treatment with thiamine in patients with septic shock remains an attractive therapeutic target. However, evidence supporting this concept is still weak, and further studies are needed before a definitive conclusion regarding the role of thiamine as a therapeutic adjunct in this setting.

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Footnote

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