



Reply to Mumin *et al.*: The Challenges of Using and Measuring Thiamine in Critical Care



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From the Authors:

We thank Drs. Mumin, McKenzie, and Spronk for their comments on our article that described a randomized trial of thiamine for kidney protection in septic shock (1, 2). They raise important points, and we appreciate the opportunity to respond and share additional background regarding certain design choices for the TRPSS (Thiamine for Renal protection in Septic Shock) trial.

The first point raised concerns about the selection of thiamine dose in TRPSS. The letter authors appropriately note that in critical illness, both the pharmacokinetics and pharmacodynamics of thiamine may be altered. We agree that the pharmacokinetics and pharmacodynamics of parenteral thiamine in sepsis are likely abnormal, and the optimal dose of thiamine is not known. The dose selected (200 mg twice daily) was chosen for consistency with our prior randomized trial of thiamine in septic shock (3). In that trial, the dose of 200 mg of thiamine rapidly and dramatically increased plasma thiamine concentrations (Figure 1). The letter authors are correct, however, that this dose may be insufficient in sepsis, especially when neurologic outcomes such as delirium are considered and adequate doses to cross the blood–brain barrier are necessary. We note, however, that even doses in routine clinical use for Wernicke’s encephalopathy are based on extremely limited data (4), and additional research regarding the dosing of thiamine in critical illness is needed.

Delirium in the TRPSS trial was measured using the Confusion Assessment Method in the Intensive Care Unit tool. The Confusion Assessment Method in the Intensive Care Unit is a validated tool for the assessment of delirium in the ICU and is measured and recorded clinically by bedside ICU nurses. Reducing delirium was not the primary focus of TRPSS; however, we agree with the letter authors that thiamine is a potential therapy for delirium attenuation in critical illness (5). A study focused on delirium may indeed opt to use a higher dose of thiamine to ensure adequate concentration across the blood–brain barrier.

Last, the optimal approach to thiamine measurement in critical illness is not known. The approach used in TRPSS is the same as that of our prior studies (3, 6–8), including the Thiamine in Septic Shock

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the concentration of hydrophilic drug (in this case, intravenous thiamine) in the central compartment—blood or plasma—is diluted, requiring a greater dosing to obtain adequate concentrations. Dose optimization and understanding of drug PKs and their influence on PDs in critical illness may be needed to ensure maximum effect. We wonder if the authors had considered the altered PKs in their dose decision for intravenous thiamine.

Second, we would be interested whether a validated delirium screening tool was used in this trial. The high prevalences of delirium in both arms may also be attributed to sepsis being a major confounder of delirium detection (4). In line with this, we wonder whether higher dosages of intravenous thiamine have resulted in detectable differences in the incidence of delirium, given the recommended intravenous doses of 500 mg or more three times per day for a thiamine-depleted brain in Wernicke’s encephalopathy.

Finally, we concur with Fujii and Sevransky in their editorial that the “gold” measurement for thiamine is indeed whole blood (5). Thiamine diphosphate, as the bioactive form of thiamine, is present in negligible amounts in plasma, whereas whole-blood thiamine makes up 80% of total circulating thiamine and is therefore a good derivative of whole-body stores of thiamine (6). Did the authors consider measuring whole-blood thiamine levels, which could have led to different conclusions of the trial? What would be their thoughts regarding the inclusion of the PK/PD parameters of intravenous thiamine, as well as whole-blood thiamine levels, in future studies of thiamine in critically ill patients? ■

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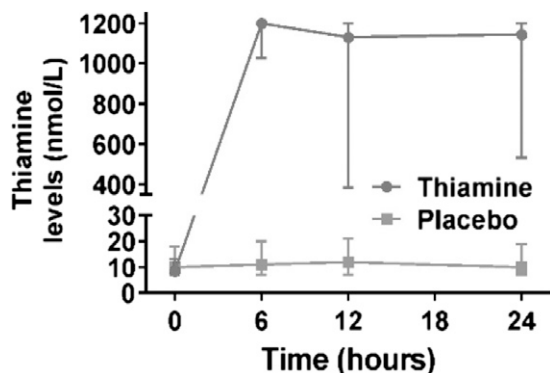


Figure 1. Plasma thiamine concentrations over time in the thiamine in septic shock trial. Values represent means, with error bars representing SDs.

trial, in which there was lower mortality in the thiamine-deficient group if thiamine was administered as compared with placebo (3). We agree that there may be advantages to measuring thiamine in whole blood, but it is also possible that this approach is more specific but less sensitive and may result in a number of patients with thiamine deficiency who are not identified. Indeed, given the results of this trial, measurement of thiamine in whole blood would have shown either similar findings (i.e., a differential effect of thiamine with greater impact in the thiamine-deficient group) or no heterogeneity of treatment effect based on thiamine concentration (perhaps confirming that whole blood may be more specific but less sensitive). Along those lines, it is not clear what thiamine concentration is adequate in sepsis, and it is possible that patients with concentrations generally considered to be in the normal range actually have thiamine deficiency.

In sum, we agree with the important points raised in the authors' letter. We look forward to growing the evidence base in thiamine supplementation during critical illness in future larger studies in which these more detailed questions can be better answered. ■

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