



Thiamine supplementation for acute heart failure patients

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This editorial refers to ‘Supplemental thiamine for the treatment of acute heart failure syndrome: a randomized controlled trial’, by Smithline *et al.*, *BMC Complementary and Alternative Medicine* 2019;19:96.

Heart failure is a leading cause of hospitalization and mortality in the United States and other Western countries (1). Despite widespread use of inhibitors of renin-angiotensin-aldosterone system, beta-blockers, and advances in device therapy, the quality of life remains poor in a large percentage of heart failure patients. Advanced heart failure is often associated with micronutrient deficiencies from poor oral intake due to cardiac cachexia, decreased gut absorption as a consequence of splanchnic congestion, altered metabolism, and increased urinary losses from diuretic therapy (2).

Thiamine (also called as vitamin B₁) is a water-soluble micronutrient that is essential for cellular energy production. The active form thiamine pyrophosphate (TPP) serves as a co-enzyme in the Krebs cycle and pentose phosphate pathway, thereby playing a vital part in the ATP production via aerobic metabolism (2). Thiamine also modulates ion channels for nerve membrane stability and efficient nerve conduction (3). Thiamine deficiency manifests as dry beriberi with neuropathy, or wet beriberi with high-output cardiac failure. Heart failure in thiamine deficiency is proposed to be a result of direct myocardial dysfunction from impaired aerobic energetics, and excessive production of lactate from anaerobic metabolism with resulting increase in venous blood return/preload to the heart (through lactate-mediated decrease in peripheral venous resistance) (4,5). Timely thiamine replacement promptly reverses cardiac failure resulting from severe

thiamine deficiency. However, there is lack of clarity on the role of thiamine supplementation in patients with heart failure not primarily resulting from thiamine deficiency.

There is some evidence that thiamine levels may be low in patients with heart failure compared to the general population. Seligmann *et al.* were among the earliest to investigate the prevalence of thiamine deficiency in heart failure patients in 1991 (6). Out of 23 heart failure patients on high dose furosemide in their study, 21 were thiamine-deficient (compared to 2 out of 16 in control group, $P < 0.001$). Similar results were obtained by Rieck *et al.* and Zenuk *et al.*, who concluded that increased urinary flow and urinary thiamine excretion was the predominant basis for thiamine deficiency in heart failure patients on diuretics (7,8). Overall, the prevalence of thiamine deficiency has varied from 3% to 91% of patients with heart failure in studies conducted in inpatient and outpatient settings (2,9).

Based on the observations of thiamine deficiency in heart failure, studies have been conducted to determine the effect of thiamine supplementation in these patients. In a small-sample study by Seligmann *et al.* (6), treatment with intravenous thiamine 100 mg twice daily for a week improved functional capacity by at least one NYHA class in all six patients and left ventricular ejection fraction (LVEF) by a mean of 13% in four of five patients evaluated by echocardiography. Pfitzenmeyer *et al.* randomized 35 heart failure patients to either receive thiamine 200 mg daily (intravenous or intramuscular) or no supplementation (10). Unlike the previous study, no difference was noted in the NYHA class or clinical status between the two groups in this trial. In another study by Shimon and colleagues (11), 30 hospitalized patients with

heart failure secondary to myocardial ischemia and on high daily dose (80 mg or more) furosemide for at least 3 months were administered either 200 mg/day intravenous thiamine or placebo for one week. The thiamine group showed improvement in LVEF on repeat echocardiogram after a week. A cross-over study by Schoenenberger *et al.* showed an improvement in LVEF in nine patients who received oral thiamine 300 mg/day for 28 days (12). DiNicantonio *et al.* performed a meta-analysis of the two trials by Shimon and Schoenenberger *et al.* (11,12), and reported that thiamine supplementation improved LVEF by mean of 3.28% compared to the placebo group (13). In their observational study, Jikrona *et al.* found that patients who received thiamine 300 mg/day for 28 days had improvement in LVEF by a mean of 13.5% compared to the control group (14). In a recent study, Mousavi randomized 52 patients with heart failure and LVEF >40% to receive either thiamine 300 mg/day or a placebo for one month, and saw no significant difference in dyspnea or echocardiographic parameters between the two groups (15).

The study by Smithline and colleagues published in the BMC complementary and alternative medicine (16) showed the benefit of thiamine therapy in acute heart failure. This was a stratified block randomized double-blinded placebo-controlled trial performed at two urban academic centers. A total of 130 patients admitted to the hospital with acute decompensated heart failure were randomized to either receive intravenous thiamine 100 mg in dextrose infusion on days 1 and 2 of admission (treatment arm) or plain dextrose infusion as placebo (control arm), in addition to standard care. The primary outcome of interest was dyspnea severity measured on a 100-mm visual analog scale (VAS) in the following positions—sitting up on oxygen, sitting up off oxygen, and lying supine off oxygen. Secondary outcomes that were measured included peak expiratory flow rate (PEFR), NT-proBNP, free fatty acid and glucose levels, length of stay, 30-day rehospitalizations and mortality. Evaluable data were obtained in 118 patients—63 in the treatment group and 55 in the control group. Despite an increase in the blood thiamine levels in the treatment group, there was no statistically significant improvement in the primary or secondary outcomes compared to the control group. Surprisingly, dyspnea severity in the sitting up position on supplemental oxygen improved to a lesser degree in the thiamine group compared to the control group, which may have been artifactual since there was no difference in dyspnea in other positions or PEFR.

This was an interesting study in patients with acute

heart failure that used a patient-centered primary outcome (dyspnea). Randomization was stratified based on NT-proBNP value to balance severity of heart failure in both groups, and diabetes medication status to account for its impact on glucose and fatty acid metabolism. However, there were several limitations to this study as acknowledged by the authors. The sample size was small which markedly limited the study's power to detect a difference. Only one subject in the thiamine group (and none in the control group) had thiamine deficiency at baseline, which was much lower than what was anticipated at the start of the trial. It is likely that the lack of benefit from thiamine was in part due to lack of thiamine deficiency in the study population, and it may be proposed that thiamine supplementation may be "beneficial" only in patients with low thiamine levels. The dose of thiamine that was used in this study was the traditional dose of 100 mg that is used to treat deficiency states. It is also possible that a higher than the standard dose of thiamine may be required to see favorable outcomes in patients with heart failure, particularly acute onset. These proposals are based on the results of a recent trial that showed the benefit of high dose (200 mg) thiamine supplementation in septic shock patients with low thiamine levels (17). In the study by Smithline and colleagues (16), there was no follow-up echocardiogram or objective documentation of ejection fraction after thiamine replacement. Additionally, the follow-up period was only 30 days. Notably, thiamine's beneficial effects on myocardial energetics may take longer to manifest. The VAS used by the authors has not been extensively used or validated. Several other more objective techniques for dyspnea assessment have been proposed in the past (18).

In essence, at present there are not enough data to support thiamine supplementation in thiamine-insufficient or sufficient acute or chronic heart failure patients. We suggest that heart failure patients particularly those on diuretics may be screened for thiamine deficiency. It is possible that thiamine supplementation in high doses may be salutary in patients with heart failure documented to be thiamine-deficient. Studies till date have yielded mixed results, and we believe that larger studies with a clear endpoints are needed to document beneficial effects in patients with acute or chronic heart failure.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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