

## Title

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3 **A multicenter randomized clinical trial of pharmacological vitamin B1**  
4 **administration to critically ill patients who develop hypophosphatemia during**  
5 **enteral nutrition (The THIAMINE 4 HYPOPHOSPHATEMIA trial)**  
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1. critical illness
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3. enteral nutrition
4. phosphate
5. refeeding syndrome
6. thiamine

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## ABSTRACT

### **Background**

Hypophosphatemia may be a useful biomarker to identify thiamine deficiency in critically ill enterally-fed patients. The objective was to determine whether intravenous thiamine affects blood lactate, biochemical and clinical outcomes in this group.

### **Method**

This randomized clinical trial was conducted across 5 Intensive Care Units. Ninety critically ill adult patients with a serum phosphate  $\leq 0.65$  mmol/L within 72 hours of commencing enteral nutrition were randomized to intravenous thiamine (200mg every 12 hours for up to 14 doses) or usual care (control). The primary outcome was blood lactate over time and data are median [IQR] unless specified.

### **Results**

Baseline variables were well balanced (thiamine: lactate 1.2 [1.0, 1.6] mmol/L, phosphate 0.56 [0.44, 0.64] mmol/L vs. control: lactate 1.0 [0.8, 1.3], phosphate 0.54 [0.44, 0.61]).

Patients randomized to the intervention received a median of 11 [7.5, 13.5] doses for a total of 2200 [1500, 2700] mg of thiamine.

1 Blood lactate over the entire 7 days of treatment was similar between groups (mean  
2 difference = -0.1 (95% CI -0.2 to 0.1) mmol/L; P=0.55). The percentage change from  
3 lactate pre-randomization to T=24 hours was not statistically different (thiamine: -32 (-  
4 39, -26) vs. control: -24 (-31, -16) percent, P=0.09). Clinical outcomes were not  
5 statistically different (days of vasopressor administration: thiamine 2 [1, 4] vs. control  
6 2 [0, 5.5] days; P=0.37, and deaths 9 (21%) vs. 5 (11%); P=0.25).  
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### 18 **Conclusions**

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21 In critically ill enterally-fed patients who developed hypophosphatemia, intravenous  
22 thiamine did not cause measurable differences in blood lactate or clinical outcomes.  
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### 29 **Trial Registration**

30 Australian and New Zealand Clinical Trials Registry (ACTRN12619000121167)  
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## INTRODUCTION

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2           Enteral nutrition is provided to the majority of patients who are admitted to the  
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4 Intensive Care Unit (ICU) (1). Patients who receive enteral nutrition frequently develop  
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6 low serum phosphate concentrations (2-5), and clinical manifestations of  
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8 hypophosphatemia may be life-threatening (6, 7).  
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15           Vitamin B1 (thiamine) is essential for producing energy from glucose via the  
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17 generation of pyruvate and conversion to acetyl coenzyme A for entry into the citric  
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19 acid (Krebs) cycle (7, 8). Accordingly, thiamine is essential to metabolise  
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21 carbohydrate. Whilst thiamine deficiency is reported as prevalent in the critically ill (9-  
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23 13), there is no current point of care measurement for plasma thiamine concentrations  
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25 (14).  
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33           Thiamine exists in multiple forms through the addition of one or more phosphate  
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35 groups: including thiamine, thiamine monophosphate, thiamine diphosphate and  
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37 thiamine triphosphate (15). Thiamine diphosphate is the principal active coenzyme  
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39 form required for entry to the citric acid cycle. It is therefore plausible that  
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41 hypophosphatemia may exacerbate adverse effects associated with thiamine  
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43 deficiency, and hypophosphatemia may be a useful biomarker to identify those at risk  
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45 of thiamine deficiency (14, 15).  
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54           When commencing a diet with a proportion of carbohydrate, consistent with  
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56 standard enteral nutrition formula used in the ICU (16), relative thiamine deficiency  
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58 can be followed by changes in intermediate metabolism that produce an increase in  
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1 lactate (17). Not only is blood lactate a robust biomarker of impaired glucose  
2 metabolism (18, 19) but increasing concentrations are strongly associated with inferior  
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4 clinical outcomes, including increased mortality (19-21).  
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10 In summary, thiamine is an essential cofactor for glucose utilization, and there  
11 is biological plausibility that phosphate deficiency may identify a cohort at greater risk  
12 of thiamine deficiency, and that these deficiencies are synergistic. Accordingly, this  
13 trial aimed to test the null hypothesis that in critically ill enterally-fed patients who  
14 develop hypophosphatemia, the administration of pharmacological doses of  
15 intravenous (IV) thiamine, when compared to standard care, would have no effect on  
16 blood lactate concentrations.  
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## 34 **MATERIALS AND METHODS**

### 35 **Trial design**

36 This was an investigator-initiated, multi-center, open-label, parallel-group,  
37 randomized clinical trial to compare pharmacological administration of thiamine (200  
38 mg IV twice daily for a maximum of seven days) to usual care (physician prescribed  
39 enteral feed) in critically ill enterally fed patients with hypophosphatemia to determine  
40 the effect on blood lactate.  
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55 The protocol was approved by the Human Research Ethics Committee of  
56 Melbourne Health, Australia (2018.283). Written informed consent for enrolment or  
57 consent to continue and use of patient data was obtained from each patient or their  
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legal surrogate. The trial was registered prospectively on the Australian and New Zealand Clinical Trials Registry (ACTRN12619000121167).

## **Study Participants**

Critically ill adult patients (aged  $\geq 18$  years) who had a reduction in their serum phosphate to 0.65 mmol/L or less within 72 hours of commencing enteral nutrition were eligible (22, 23). Patients were excluded if they had already received 100 mg or more of thiamine in the previous 48 hours, were anticipated to be discharged from ICU by the end of the following day, if the treating clinician believed that either treatment was in the best interest of the patient (e.g. established refeeding syndrome), patients receiving end-of-life care or admitted for organ donation, those who were pregnant, previously enrolled in this trial, had known hypersensitivity to thiamine or latex allergy, and any patient with suspected beri-beri disease or Wernicke's encephalopathy. Given that severe hypophosphatemia may represent a cohort with greater metabolic dysfunction, a threshold of 0.32 mmol/L was chosen *a priori* to identify those with severe hypophosphatemia (6, 23). Additional baseline characteristics were subsequently obtained including recent weight loss and negligible nutrient intake in the preceding 5 days (24, 25).

## **Study randomization and treatment**

The random allocation sequence was generated by the statistical coordination center (University of Adelaide) using computer-generated random numbers with permuted block sizes of 2, 4, and 6 stratified by study site and phosphate concentrations  $< 0.32$  mmol/L. The sequence was then embedded into the Research

1 Electronic Data Capture (REDCap) system, a secure web application for managing  
2 online data collection. Randomization was performed using the REDCap system at  
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4 each study site with the allocation sequence concealed from all investigators and sites  
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6 enrolling patients.  
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## 10 11 12 **Data capture**

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16 Data were collected using paper case report forms and entered into REDCap  
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18 at each site (26). A data dictionary was provided to each site (Supplemental Material).  
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## 24 **Intervention and comparator**

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27 Both groups received thiamine from standard liquid enteral formula used in  
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29 routine clinical practice at participating sites as prescribed by the treating clinician;  
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31 these typically contained between 1.5-3.6 mg/L of thiamine. The 'control group'  
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33 received no additional thiamine, enteral or IV.  
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40 Patients in the intervention or 'thiamine group' received IV thiamine (Biological  
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42 Therapies, Braeside Vic) 200mg every 12 hours. Thiamine was added to 100mL  
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44 sodium chloride 0.9% and infused over 30 minutes. The intervention was ceased if the  
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46 participant: had tube enteral feeding discontinued for 12 hours with no plans to  
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48 recommence within the next 12 hours, no longer had IV access, was discharged alive  
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50 from ICU, received 7 days of treatment (i.e., maximum 14 doses), or died.  
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1 All co-interventions, such as phosphate replacement and nutrition (23),  
2 occurred as per standard care directed by the treating clinician.  
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## 8 **Outcomes**

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10 The primary outcome was arterial blood lactate. Arterial blood gases were  
11 recorded 6-hourly for 7 days in those with an arterial catheter. Given blood lactate was  
12 anticipated to trend to normal over time in all patients who survived, the predominant  
13 effect upon lactate was anticipated in the first 24 hours of treatment and so this epoch  
14 was identified as a co-primary outcome in addition to the 7 day study period.  
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## 26 ***Biochemical outcomes***

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28 Secondary biochemical outcomes including pH, blood glucose concentrations,  
29 glucose to lactate ratio, and serum phosphate and creatinine concentrations were  
30 recorded.  
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## 38 ***Co-administered interventions***

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40 Co-administered interventions such as enteral nutrition, calculated enteral  
41 thiamine, phosphate and insulin were recorded.  
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## 48 ***Clinical outcomes***

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50 The number of days of vasopressor therapy, censored at 7 days, was the major  
51 clinical outcome of interest. Patients who were not receiving vasopressor therapy at  
52 randomization were excluded from this analysis. Clinical outcomes included hospital  
53 mortality and number of days of admission censored at day 90.  
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3 **Statistical analyses**  
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6 Data are summarized as mean (standard deviation, SD), median [interquartile  
7 range, IQR] or difference (with 95% confidence intervals, CIs), with between-group  
8 differences reported by t-test, rank-sum test, or chi-squared test as indicated.  
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10 Differences in temporal profiles were assessed by generalized estimating equations  
11 regression, employing robust standard errors to allow for within-subject correlation,  
12 with between group differences reported as the mean with 95% CIs and plotted as the  
13 temporal mean profiles. Interaction effects between plasma lactate, glucose,  
14 phosphate and pH were explored by assignment group.  
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28 For the co-primary outcome, plasma lactate was analyzed as the absolute and  
29 relative change per hour from baseline, taken at 24 hours or when last measured in  
30 those with length of stay less than 24 hours. Between-group differences were analyzed  
31 by t-test and reported as the difference with corresponding P-values. Days of  
32 vasopressor therapy are reported both as the absolute number and as the proportion  
33 of study days received, with between group differences by rank-sum test. The  
34 significance level was set at 0.05 with no adjustment for multiple comparisons  
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48 Analysis were performed in Stata/MP 16.1®.  
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54 **Sample size**  
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57 The sample size was calculated using published data from Donnino and  
58 colleagues who reported blood lactate in patients with septic shock receiving thiamine  
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1 (27). Assuming that mean was equal to median and standard deviation equal to the  
2 interquartile range divided by 1.3, the difference in blood lactate at 24 hours between  
3 groups was estimated at 25%. Using Satterthwaite's t test for unequal variances, 72  
4 participants were required for a two-sided  $\alpha$  error of 0.05 and  $\beta$  error of 0.2 to detect a  
5 difference between groups of 25% or more, but to allow for dropouts and missing data  
6 the number of participants was inflated by  $\approx$  20% to 90 participants.  
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## 18 **RESULTS**

### 19 **Study participants**

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Between March 2019 and December 2020, 380 patients from five ICUs met all inclusion criteria with 90 patients meeting no exclusion criterion and randomized (Figure 1).

The study participants were well balanced in terms of baseline characteristics, pre-randomization treatments and biochemistry (Table 1 and Table S1, Supplementary Material). The majority of participants did not have risk factors on clinical history that would have identified a high risk of refeeding syndrome (Table 1).

### 66 **Study treatment**

At least 1 dose of exogenous thiamine was administered to every participant assigned to the intervention, and at no stage during ICU admission did a participant in the control group receive IV thiamine. The time from admission to randomization was similar between groups (median time from ICU admission to randomization, thiamine:

1 51 [35, 71] hours and control: 52 [42, 70] hours). Once randomized to the intervention  
2 group, participants received thiamine within 9 [1, 12] hours. Participants in the  
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4 intervention group received study treatment for a median of 11 [7.5, 13.5] doses with  
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6 mean IV administration of 371 [333, 400] mg/day for a mean total IV dose of 2200  
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8 [1500, 2700] mg of thiamine.  
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### 11 12 13 14 15 **Co-administered treatments** 16

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18 The median [IQR] total days of enteral nutrition were similar between groups (thiamine:  
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20 6 [4, 7] vs. control: 5 [3, 7] days; P=0.22] as were volume of enteral nutrition (1041  
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22 [735, 1306] vs. 882 [777, 1164] mL/day; P=0.25), carbohydrates (144 [101, 185] vs.  
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24 119 [60, 158] g/day; P=0.06) and energy (1264 [893, 1632] vs. 1050 [525, 1395]  
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26 kcal/day; P=0.07).  
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32 The amount of enteral thiamine provided in nutrition formula was similar between  
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34 groups (12.1 [5.9, 15.1] vs 8.9 [4.6, 14.7] mg; P=0.23) but the total (IV + enteral) dose  
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36 of thiamine administered was substantially greater in the intervention group (2215  
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38 [1509, 2717] vs. 8.9 [4.6, 14.7] mg; P<0.01).  
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47 Phosphate administration was similar between groups (Table S2 and Figures S1 and  
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49 S2, Supplemental Material). A similar number of patients received insulin (20 (46%)  
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51 vs. 20 (44%); P=0.85) but the mean daily dose of insulin was substantially greater in  
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53 the intervention group (41 [19, 94] vs. 13 [3, 44] units/day; P=0.02).  
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3 **Primary Outcome**  
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6 The blood lactate concentrations over the 7-day time period were similar  
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8 between groups (1.2 (95% CI 1.1 to 1.3) mmol/L vs. 1.3 (1.1 to 1.4) mmol/L; difference  
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10 -0.1 (-0.2 to 0.1) mmol/L; P=0.55; Figure 2). There was no statistical difference in blood  
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12 lactate against time gradient in the first 24 hours (-0.02 (-0.03, -0.02) vs. -0.02 (-0.03,  
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14 -0.01) mmol/L/hour, P=0.32), nor in the relative change from baseline at 24 hours (-32  
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16 (-39, -26) vs. -24 (-31, -16) percent; P=0.09).  
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26 **Biochemical Outcomes**  
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29 Serum phosphate concentrations increased over time and were similar in both  
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31 groups (Figure S3, Supplemental Material). All other biochemical outcomes (pH,  
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33 glucose and creatinine) were similar between groups (Figures S4 –S6, Supplemental  
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35 Material)  
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42 **Clinical outcomes**  
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45 Days of vasopressor therapy was similar between groups (2 [1, 4] versus 2 [0,  
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47 5.5] days, P=0.37). Hospital mortality (9 (21%) vs. 5 (11%); P=0.25) and duration of  
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49 hospital admission were also not statistically different between groups (20 [11, 26] vs.  
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51 20 [11, 36] days; P=0.96)  
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## Subgroup analysis

To assess whether results were affected by relatively low blood lactate at randomization post hoc analyses were conducted. Inferences did not vary according to lactate at randomization ( $P=0.89$ ) or for those with a lactate  $> 2.0$  mmol/L at randomization ( $P=0.33$ ). There were insufficient numbers of patients with admission diagnosis of septic shock ( $n=5$ ) or severe hypophosphatemia at randomization ( $n=7$ ) to analyze.

## Adverse Events

There were no adverse events reported with the use of IV thiamine.

## DISCUSSION

The major observation from this trial is that the administration of IV thiamine to critically ill patients who developed hypophosphatemia during enteral nutrition administration did not result in detectable differences in blood lactate or any measured biochemical or clinical outcome.

Severe metabolic disturbances occur in patients with refeeding syndrome. Indeed, severe hypophosphatemia in patients with risk factors is considered the pathognomonic feature of the syndrome (28, 29). In patients with established refeeding syndrome, treatment with phosphate replacement, thiamine administration and calorie restriction is accepted as a standard of care (28). However, most episodes of hypophosphatemia associated with commencing enteral nutrition occur in patients

1 with no risk factors for, or additional clinical features of, refeeding syndrome (2, 4). The  
2 incretin hormone secretion secondary to enteral nutrient stimulates insulin secretion  
3 causing marked intracellular shift of phosphate, which requires exogenous  
4 supplementation of phosphate (30). In this trial, study participants had  
5 hypophosphatemia but none were identified by the treating clinical team as having the  
6 refeeding syndrome, with hypophosphatemia used as a biomarker to identify a cohort  
7 of patients who may be at risk of thiamine deficiency – with the assumption that  
8 pharmacological thiamine administration is more likely to benefit those who are  
9 deficient.  
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25 Whilst thiamine is reported by health care workers to be the most frequently  
26 administered vitamin in the ICU (7), there are only sparse data evaluating the efficacy  
27 of pharmacological thiamine administration during critical illness. Prior to the current  
28 study, the only randomized clinical trial that evaluated thiamine as a stand-alone  
29 treatment included 88 patients with sepsis from two ICUs (27). Administration of 200  
30 mg of thiamine twice daily was compared to usual care and, in the subgroup of patients  
31 who were subsequently identified as having thiamine-deficiency, the intervention  
32 reduced plasma lactate concentrations, improved renal function, and reduced  
33 mortality (27, 31). While results from this randomized clinical trial are supported by  
34 observations in cohort studies (17, 32) there is no current methodology to rapidly  
35 quantify plasma thiamine concentrations.  
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## 55 **Limitations**

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The major limitation of this trial was the open-label design. This was a pragmatic decision as the trial was only supported with seed funding and the cost of blinding an identifiable solution such as thiamine across multiple sites was prohibitive. Moreover, the primary outcome (blood lactate) is resistant to researcher bias. Nonetheless, the open label design increases the risk of investigators influencing results with confounding treatments. Co-interventions include nutritional therapy, which was not protocolized, and there is expert opinion that calorie restriction is beneficial in the acute phase of critical illness, particularly in patients who develop hypophosphatemia (22, 23, 33-36). However, there was greater, albeit not statistically significant, volume, carbohydrate and energy delivery in the group assigned to thiamine, which suggests that investigators and clinicians were not surreptitiously manipulating non-trial interventions to influence clinical outcomes. Another co-intervention was phosphate administration. Whilst there were no statistical differences in phosphate administration (Table S2 and Figure S1) and plasma phosphate concentrations (Figure S3) between groups, an effect of thiamine, if one exists, may have been more apparent if phosphate administration had been restricted in both groups.

This trial contained other limitations that should be acknowledged. Because of a lack of point-of-care testing to identify thiamine deficiency, this trial utilized a strategy of predictive enrichment with serum phosphate to identify a cohort that may benefit from thiamine administration (37). Whilst there is a biological rationale for this approach, there is no established association between hypophosphataemia and thiamine deficiency. Moreover, there was a trade off in terms of prognostic enrichment – i.e. an increased blood lactate was not an eligibility criterion. Accordingly, the current study did not evaluate whether patients with established thiamine deficiency and/or

1 increased blood lactate benefit from pharmacological administration of thiamine.  
2 Moreover, whilst there was no signal of patient-centered benefit with the intervention,  
3 these were only exploratory outcomes due to the small size of the cohort, and there  
4 may be important differences that were undetected. The sample size was based on a  
5 trial of patients in septic shock and was calculated to detect a between group  
6 difference in blood lactate of 25% or more. However, using these data for the sample  
7 size calculation for a trial of patients that did not have septic shock, risks missing a  
8 smaller but still clinically meaningful difference. Accordingly, this trial did not evaluate  
9 whether IV thiamine is a useful intervention in patients with septic shock and/or  
10 profound lactic acidosis (38, 39).  
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## 27 **Clinical impact**

28 The implication for clinical practice is that thiamine supplementation does not  
29 appear to reduce blood lactate or be of substantial clinical benefit in this unselected  
30 sample population. Given the expense incurred with acquiring and administering  
31 thiamine, the use of thiamine should be limited to those suspected on clinical  
32 assessment to be at risk for thiamine deficiency or refeeding syndrome. Whether those  
33 at high risk of relative or absolute thiamine deficiency can be rapidly identified by other  
34 point of care techniques requires further evaluation (40).  
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## 51 **Conclusions**

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In critically ill enterally-fed patients who develop hypophosphatemia without prominent features of thiamine deficiency, the pharmacological administration of thiamine has no effect on blood lactate.

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## REFERENCES

1. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, et al: Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med* 2017; 43(3):380-398
2. Berger MM, Appelberg O, Reintam-Blaser A, Ichai C, et al: Prevalence of hypophosphatemia in the ICU - Results of an international one-day point prevalence survey. *Clin Nutr* 2020
3. Reintam Blaser A, Gunst J, Ichai C, Casaer MP, et al: Hypophosphatemia in critically ill adults and children - A systematic review. *Clin Nutr* 2020
4. Reintam Blaser A, van Zanten ARH: Electrolyte disorders during the initiation of nutrition therapy in the ICU. *Curr Opin Clin Nutr Metab Care* 2021; 24(2):151-158
5. Chapman M, Peake SL, Bellomo R, Davies A, et al: Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. *N Engl J Med* 2018; 379(19):1823-1834
6. Camp MA, Allon M: Severe hypophosphatemia in hospitalized patients. *Miner Electrolyte Metab* 1990; 16(6):365-368
7. Vankrunkelsven W, Gunst J, Amrein K, Bear DE, et al: Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: The VITA-TRACE survey. *Clin Nutr* 2021; 40(2):590-599
8. Moskowitz A, Donnino MW: Thiamine (vitamin B1) in septic shock: a targeted therapy. *J Thorac Dis* 2020; 12(Suppl 1):S78-S83
9. Donnino MW, Carney E, Cocchi MN, Barbash I, et al: Thiamine deficiency in critically ill patients with sepsis. *J Crit Care* 2010; 25(4):576-581
10. Costa NA, Gut AL, de Souza Dorna M, Pimentel JA, et al: Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. *J Crit Care* 2014; 29(2):249-252
11. van Snippenburg W, Reijnders MGJ, Hofhuis JGM, de Vos R, et al: Thiamine Levels During Intensive Insulin Therapy in Critically Ill Patients. *Journal of Intensive Care Medicine* 2017; 32(9):559-564
12. Gundogan K, Akbudak IH, Bulut K, Temel S, et al: Thiamin Status in Adults Receiving Chronic Diuretic Therapy Prior to Admission to a Medical Intensive Care Unit: A Pilot Study. *Nutr Clin Pract* 2019; 34(4):565-571
13. Berger MM, Manzanares W: Micronutrients early in critical illness, selective or generous, enteral or intravenous? *Curr Opin Clin Nutr Metab Care* 2021; 24(2):165-175
14. Fujii T, Deane AM, Nair P: Metabolic support in sepsis: corticosteroids and vitamins: the why, the when, the how. *Curr Opin Crit Care* 2020; 26(4):363-368
15. Collie JTB, Greaves RF, Jones OAH, Lam Q, et al: Vitamin B1 in critically ill patients: needs and challenges. *Clin Chem Lab Med* 2017; 55(11):1652-1668
16. Ridley EJ, Peake SL, Jarvis M, Deane AM, et al: Nutrition Therapy in Australia and New Zealand Intensive Care Units: An International Comparison Study. *JPEN J Parenter Enteral Nutr* 2018; 42(8):1349-1357
17. Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, et al: Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients With Septic Shock. *Crit Care Med* 2018; 46(11):1747-1752
18. Kaukonen KM, Bailey M, Egi M, Orford N, et al: Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. *Crit Care Med* 2014; 42(6):1379-1385

19. Hernandez G, Bellomo R, Bakker J: The ten pitfalls of lactate clearance in sepsis. *Intensive Care Medicine* 2019; 45(1):82-85
20. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, et al: Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37(5):1670-1677
21. Chebl RB, Tamim H, Dagher GA, Sadat M, et al: Serum Lactate as an Independent Predictor of In-Hospital Mortality in Intensive Care Patients. *J Intensive Care Med* 2020; 35(11):1257-1264
22. Olthof LE, Koekkoek W, van Setten C, Kars JCN, et al: Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. *Clin Nutr* 2018; 37(5):1609-1617
23. Doig GS, Simpson F, Heighes PT, Bellomo R, et al: Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med* 2015; 3(12):943-952
24. Boot R, Koekkoek K, van Zanten ARH: Refeeding syndrome: relevance for the critically ill patient. *Curr Opin Crit Care* 2018; 24(4):235-240
25. Reintam Blaser A, Rice TW, Deane AM: Update on nutritional assessment and therapy in critical care. *Curr Opin Crit Care* 2020; 26(2):197-204
26. Harris PA, Taylor R, Minor BL, Elliott V, et al: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
27. Donnino MW, Andersen LW, Chase M, Berg KM, et al: Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. *Crit Care Med* 2016; 44(2):360-367
28. McKnight CL, Newberry C, Sarav M, Martindale R, et al: Refeeding Syndrome in the Critically Ill: a Literature Review and Clinician's Guide. *Curr Gastroenterol Rep* 2019; 21(11):58
29. Ribeiro AC, Dock-Nascimento DB, Silva JM, Jr., Caporossi C, et al: Hypophosphatemia and risk of refeeding syndrome in critically ill patients before and after nutritional therapy. *Rev Assoc Med Bras (1992)* 2020; 66(9):1241-1246
30. Plummer MP, Hermanides J, Deane AM: Incretin Physiology and Pharmacology in the Intensive Care Unit. *Crit Care Clin* 2019; 35(2):341-355
31. Moskowitz A, Andersen LW, Cocchi MN, Karlsson M, et al: Thiamine as a Renal Protective Agent in Septic Shock. A Secondary Analysis of a Randomized, Double-Blind, Placebo-controlled Trial. *Ann Am Thorac Soc* 2017; 14(5):737-741
32. Holmberg MJ, Moskowitz A, Patel PV, Grossestreuer AV, et al: Thiamine in septic shock patients with alcohol use disorders: An observational pilot study. *J Crit Care* 2018; 43:61-64
33. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, et al: Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med* 2015; 372(25):2398-2408
34. Lheureux O, Preiser JC: Is slower advancement of enteral feeding superior to aggressive full feeding regimens in the early phase of critical illness. *Curr Opin Clin Nutr Metab Care* 2020; 23(2):121-126
35. van Zanten ARH, De Waele E, Wischmeyer PE: Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care* 2019; 23(1):368
36. Arabi YM, Al-Dorzi HM: Trophic or full nutritional support? *Curr Opin Crit Care* 2018; 24(4):262-268

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37. Wernerman J, Christopher KB, Annane D, Casaer MP, et al: Metabolic support in the critically ill: a consensus of 19. *Crit Care* 2019; 23(1):318
  38. Fujii T, Luethi N, Young PJ, Frei DR, et al: Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA* 2020; 323(5):423-431
  39. Sevransky JE, Rothman RE, Hager DN, Bernard GR, et al: Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA* 2021; 325(8):742-750
  40. Arabi YM, Casaer MP, Chapman M, Heyland DK, et al: The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017; 43(9):1239-1256

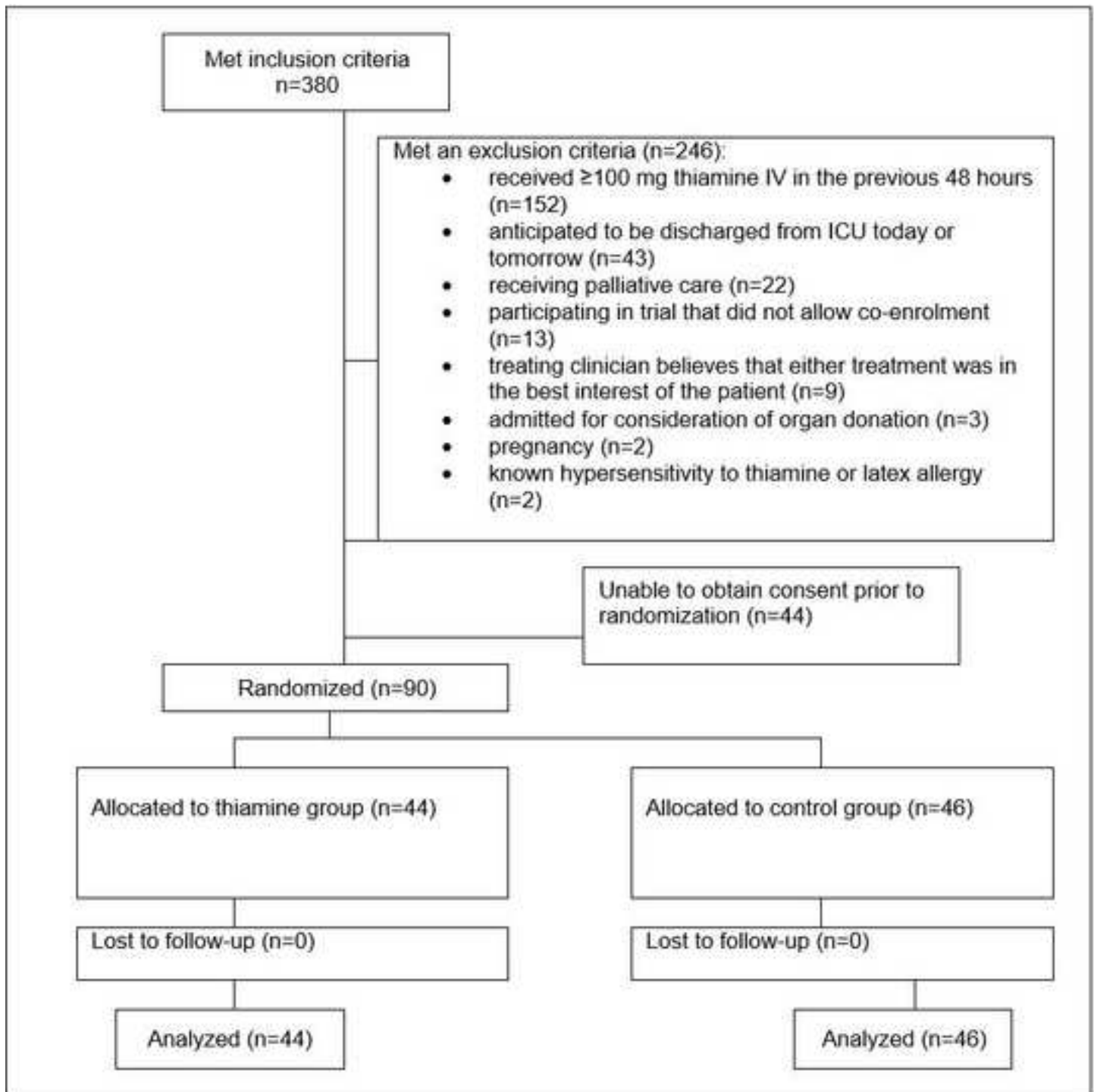
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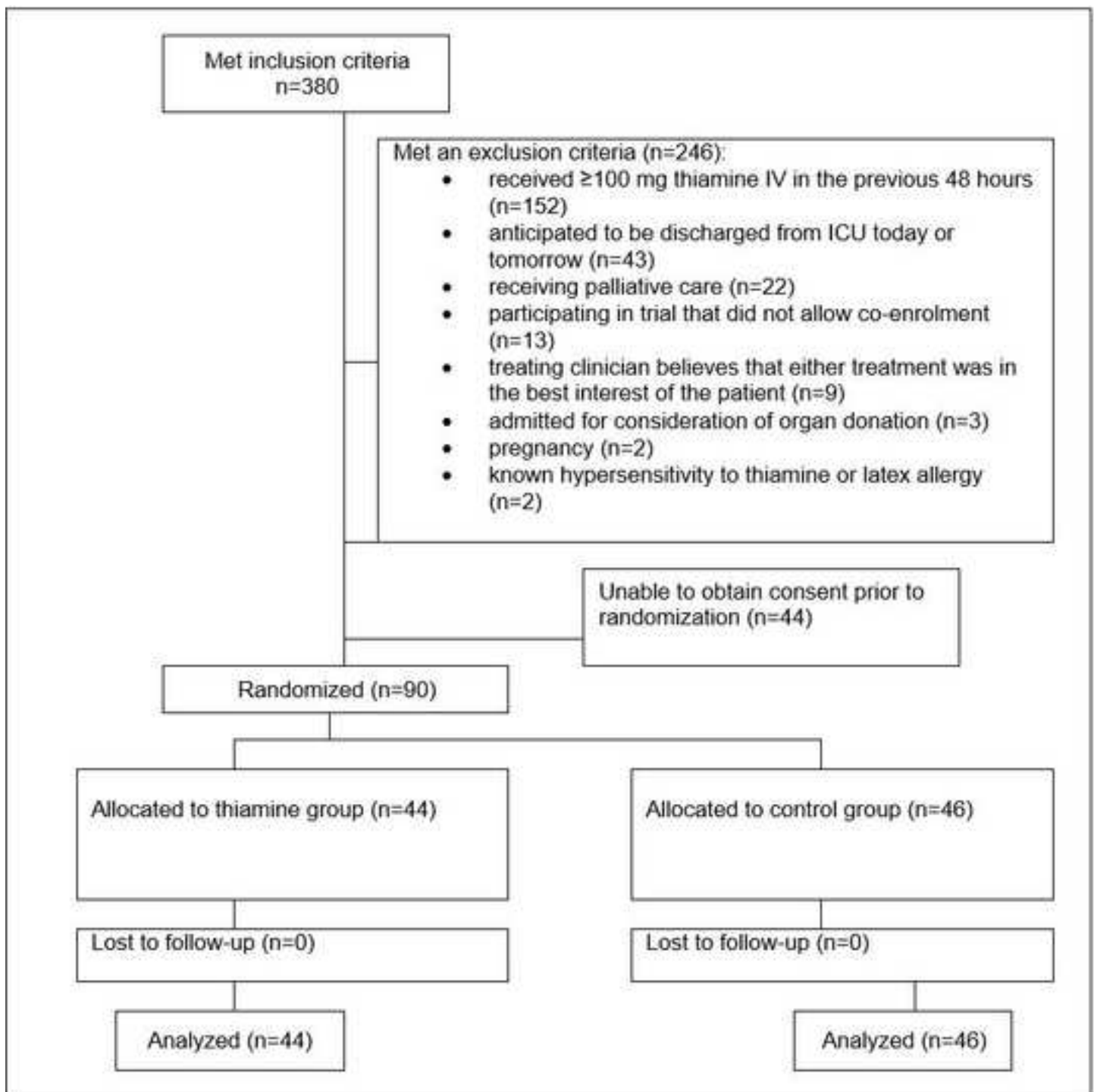
1  
2 A.M.D was responsible for trial conceptualization, methodology, obtaining resources,  
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4 funding, conducting the trial, analysis and drafting the manuscript; A.J was responsible  
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6 for trial conceptualization, methodology, conducting the trial, analysis and critical  
7  
8 revision of the manuscript; B.T and A.C were responsible for conducting the trial,  
9  
10 project administration and critical revision of the manuscript; M.E.F was responsible  
11  
12 for trial conceptualization, methodology, funding, data resources, statistical analysis  
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14 and critical revision of the manuscript; J.T.C and M.J.M. were responsible for trial  
15  
16 conceptualization, methodology, funding and critical revision of the manuscript; R.G,  
17  
18 A.N and T.F. were responsible for trial conceptualization, methodology, conducting the  
19  
20 trial and critical revision of the manuscript ; K.B., J.S.D, A.A.U, M.Y, G.R, K.F. M.J.P,  
21  
22 F.Y were responsible for conducting the trial and critical revision of the manuscript;  
23  
24 and R.B and Y.A were responsible for trial conceptualization, methodology, obtaining  
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26 resources, funding, conducting the trial, analysis and critical revision of the manuscript.  
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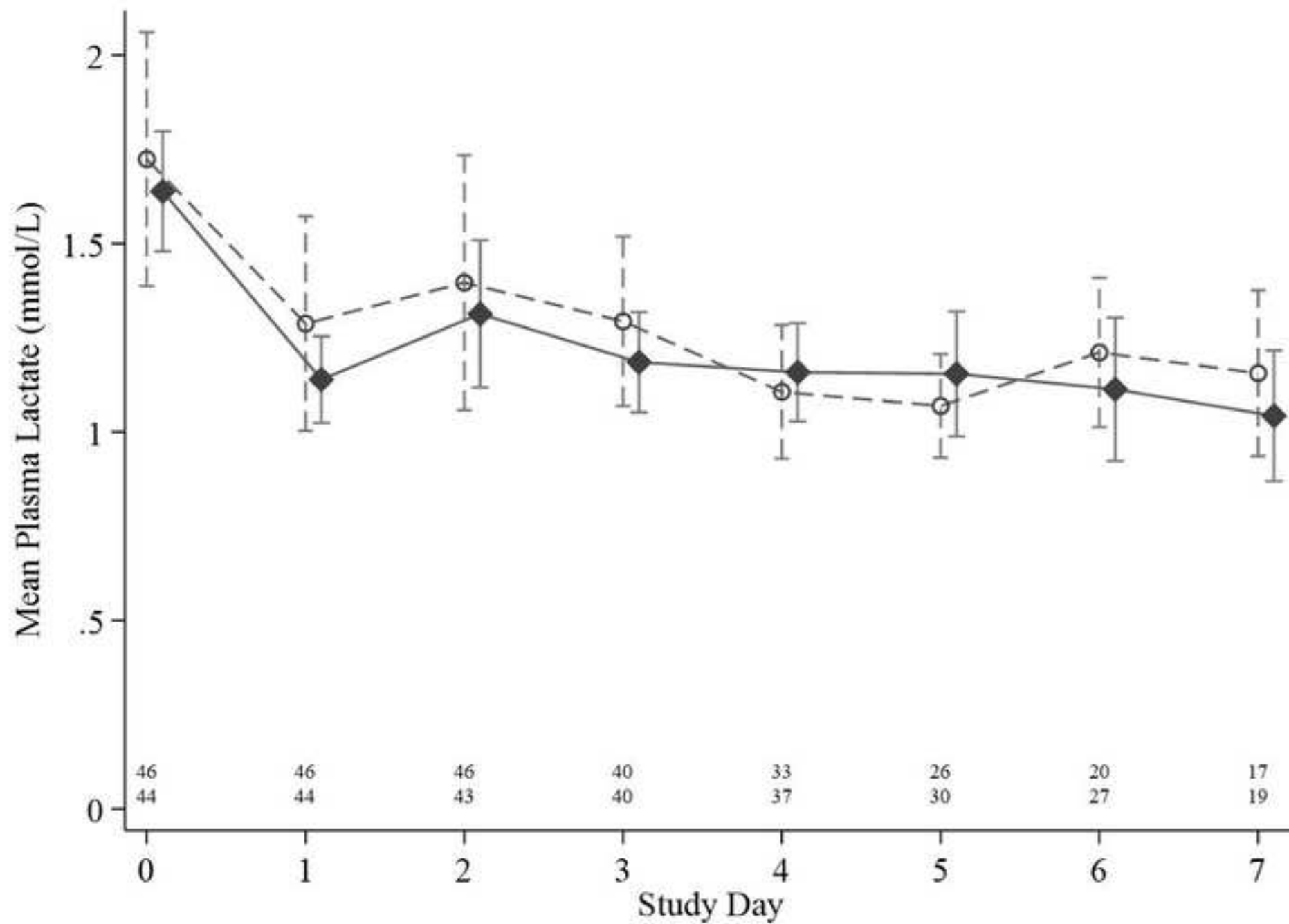
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**Figure 1.** CONSORT flow diagram

**Figure 2.** Mean plasma lactate levels, with 95% confidence intervals for the mean, by study group for days 1-7. Thiamine group shown as solid line and diamonds, control group as dashed line and open circles. The numbers of patients per group each day are shown above the x-axis, control above and thiamine below.







**Table 1. Demographic details by Randomization group**

IQR = interquartile range, APACHE = Acute Physiological and Chronic Health Evaluation, ICU = Intensive Care Unit

<b>Variable</b>	<b>Thiamine n=44</b>	<b>Control n=46</b>
Age (years), median [IQR]	50 [36, 67]	56 [40, 70]
Gender (male), n (%)	25 (57)	33 (72)
Body Mass Index (kg/m <sup>2</sup> ), median [IQR]	28.8 [25.2, 32.4]	30.0 [24.0, 31.2]
APACHE-III Score, median [IQR]	63 [41, 84]	58 [46, 81]
Weight loss past 3-6 months, n (%)		
< 5%	25 (57)	17 (39)
5-10%	2 (4.5)	1 (2.3)
> 10%	0 (0)	1 (2.3)
No score	17 (39)	25 (57)
Negligible intake ≥ 5 days, n (%)	0 (0)	1 (2.2)
<b>Pre-Randomization Therapy</b>		
Vasopressor therapy, n (%)	28 (64)	35 (76)
Mechanical ventilation, n (%)	43 (98)	44 (96)
Renal replacement therapy within 1 hour, n (%)	4 (9.1)	3 (6.5)
<b>Pre-Randomization Biochemistry</b>		
Most recent blood lactate mmol/L, median [IQR]	1.2 [1.0, 1.6]	1.0 [0.8, 1.3]
Most recent pH, median [IQR]	7.44 [7.40, 7.47]	7.42 [7.39, 7.45]
Most recent serum phosphate mmol/L, median [IQR]	0.56 [0.44, 0.64]	0.54 [0.44, 0.61]
Lowest serum phosphate (last 24 hrs) mmol/L, median [IQR]	0.53 [0.42, 0.61]	0.53 [0.44, 0.61]
Serum phosphate < 0.32 mmol/L, n (%)	4 (9.1)	3 (6.5)



## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4&5
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6&7
	2b	Specific objectives or hypotheses	6&7
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8&9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	11&12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	8&9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8&9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8&9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
Statistical methods	11b	If relevant, description of the similarity of interventions	N/A
	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	15
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 and S1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12 & Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	15
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16&17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

## Title

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3 **A multicenter randomized clinical trial of pharmacological vitamin B1**  
4 **administration to critically ill patients who develop hypophosphatemia during**  
5 **enteral nutrition (The THIAMINE 4 HYPOPHOSPHATEMIA trial)**  
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## Keywords

1. critical illness
2. acidosis, lactic
3. enteral nutrition
4. phosphate
5. refeeding syndrome
6. thiamine

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Main text: 2734 words

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The authors have disclosed there are no potential conflicts of interest.

## ABSTRACT

### **Background**

Hypophosphatemia may be a useful biomarker to identify thiamine deficiency in critically ill enterally-fed patients. The objective was to determine whether intravenous thiamine affects blood lactate, biochemical and clinical outcomes in this group.

### **Method**

This randomized clinical trial was conducted across 5 Intensive Care Units. Ninety critically ill adult patients with a serum phosphate  $\leq 0.65$  mmol/L within 72 hours of commencing enteral nutrition were randomized to intravenous thiamine (200mg every 12 hours for up to 14 doses) or usual care (control). The primary outcome was blood lactate over time and data are median [IQR] unless specified.

### **Results**

Baseline variables were well balanced (thiamine: lactate 1.2 [1.0, 1.6] mmol/L, phosphate 0.56 [0.44, 0.64] mmol/L vs. control: lactate 1.0 [0.8, 1.3], phosphate 0.54 [0.44, 0.61]).

Patients randomized to the intervention received a median of 11 [7.5, 13.5] doses for a total of 2200 [1500, 2700] mg of thiamine.

1 Blood lactate over the entire 7 days of treatment was similar between groups (mean  
2 difference = -0.1 (95% CI -0.2 to 0.1) mmol/L; P=0.55). The percentage change from  
3 lactate pre-randomization to T=24 hours was not statistically different (thiamine: -32 (-  
4 39, -26) vs. control: -24 (-31, -16) percent, P=0.09). Clinical outcomes were not  
5 statistically different (days of vasopressor administration: thiamine 2 [1, 4] vs. control  
6 2 [0, 5.5] days; P=0.37, and deaths 9 (21%) vs. 5 (11%); P=0.25).  
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### 18 **Conclusions**

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21 In critically ill enterally-fed patients who developed hypophosphatemia, intravenous  
22 thiamine did not cause measurable differences in blood lactate or clinical outcomes.  
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### 29 **Trial Registration**

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31 Australian and New Zealand Clinical Trials Registry (ACTRN12619000121167)  
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## INTRODUCTION

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2           Enteral nutrition is provided to the majority of patients who are admitted to the  
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4 Intensive Care Unit (ICU) (1). Patients who receive enteral nutrition frequently develop  
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6 low serum phosphate concentrations (2-5), and clinical manifestations of  
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8 hypophosphatemia may be life-threatening (6, 7).  
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15           Vitamin B1 (thiamine) is essential for producing energy from glucose via the  
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17 generation of pyruvate and conversion to acetyl coenzyme A for entry into the citric  
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19 acid (Krebs) cycle (7, 8). Accordingly, thiamine is essential to metabolise  
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21 carbohydrate. Whilst thiamine deficiency is reported as prevalent in the critically ill (9-  
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23 13), there is no current point of care measurement for plasma thiamine concentrations  
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25 (14).  
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33           Thiamine exists in multiple forms through the addition of one or more phosphate  
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35 groups: including thiamine, thiamine monophosphate, thiamine diphosphate and  
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37 thiamine triphosphate (15). Thiamine diphosphate is the principal active coenzyme  
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39 form required for entry to the citric acid cycle. It is therefore plausible that  
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41 hypophosphatemia may exacerbate adverse effects associated with thiamine  
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43 deficiency, and hypophosphatemia may be a useful biomarker to identify those at risk  
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45 of thiamine deficiency (14, 15).  
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54           When commencing a diet with a proportion of carbohydrate, consistent with  
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56 standard enteral nutrition formula used in the ICU (16), relative thiamine deficiency  
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58 can be followed by changes in intermediate metabolism that produce an increase in  
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1 lactate (17). Not only is blood lactate a robust biomarker of impaired glucose  
2 metabolism (18, 19) but increasing concentrations are strongly associated with inferior  
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4 clinical outcomes, including increased mortality (19-21).  
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10 In summary, thiamine is an essential cofactor for glucose utilization, and there  
11 is biological plausibility that phosphate deficiency may identify a cohort at greater risk  
12 of thiamine deficiency, and that these deficiencies are synergistic. Accordingly, this  
13 trial aimed to test the null hypothesis that in critically ill enterally-fed patients who  
14 develop hypophosphatemia, the administration of pharmacological doses of  
15 intravenous (IV) thiamine, when compared to standard care, would have no effect on  
16 blood lactate concentrations.  
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## 34 **MATERIALS AND METHODS**

### 35 **Trial design**

36 This was an investigator-initiated, multi-center, open-label, parallel-group,  
37 randomized clinical trial to compare pharmacological administration of thiamine (200  
38 mg IV twice daily for a maximum of seven days) to usual care (physician prescribed  
39 enteral feed) in critically ill enterally fed patients with hypophosphatemia to determine  
40 the effect on blood lactate.  
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55 The protocol was approved by the Human Research Ethics Committee of  
56 Melbourne Health, Australia (2018.283). Written informed consent for enrolment or  
57 consent to continue and use of patient data was obtained from each patient or their  
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legal surrogate. The trial was registered prospectively on the Australian and New Zealand Clinical Trials Registry (ACTRN12619000121167).

## **Study Participants**

Critically ill adult patients (aged  $\geq 18$  years) who had a reduction in their serum phosphate to 0.65 mmol/L or less within 72 hours of commencing enteral nutrition were eligible (22, 23). Patients were excluded if they had already received 100 mg or more of thiamine in the previous 48 hours, were anticipated to be discharged from ICU by the end of the following day, if the treating clinician believed that either treatment was in the best interest of the patient (e.g. established refeeding syndrome), patients receiving end-of-life care or admitted for organ donation, those who were pregnant, previously enrolled in this trial, had known hypersensitivity to thiamine or latex allergy, and any patient with suspected beri-beri disease or Wernicke's encephalopathy. Given that severe hypophosphatemia may represent a cohort with greater metabolic dysfunction, a threshold of 0.32 mmol/L was chosen *a priori* to identify those with severe hypophosphatemia (6, 23). Additional baseline characteristics were subsequently obtained including recent weight loss and negligible nutrient intake in the preceding 5 days (24, 25).

## **Study randomization and treatment**

The random allocation sequence was generated by the statistical coordination center (University of Adelaide) using computer-generated random numbers with permuted block sizes of 2, 4, and 6 stratified by study site and phosphate concentrations  $< 0.32$  mmol/L. The sequence was then embedded into the Research

1 Electronic Data Capture (REDCap) system, a secure web application for managing  
2 online data collection. Randomization was performed using the REDCap system at  
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4 each study site with the allocation sequence concealed from all investigators and sites  
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6 enrolling patients.  
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## 10 11 12 **Data capture**

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16 Data were collected using paper case report forms and entered into REDCap  
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18 at each site (26). A data dictionary was provided to each site (Supplemental Material).  
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## 24 **Intervention and comparator**

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27 Both groups received thiamine from standard liquid enteral formula used in  
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29 routine clinical practice at participating sites as prescribed by the treating clinician;  
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31 these typically contained between 1.5-3.6 mg/L of thiamine. The 'control group'  
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33 received no additional thiamine, enteral or IV.  
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40 Patients in the intervention or 'thiamine group' received IV thiamine (Biological  
41  
42 Therapies, Braeside Vic) 200mg every 12 hours. Thiamine was added to 100mL  
43  
44 sodium chloride 0.9% and infused over 30 minutes. The intervention was ceased if the  
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46 participant: had tube enteral feeding discontinued for 12 hours with no plans to  
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48 recommence within the next 12 hours, no longer had IV access, was discharged alive  
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50 from ICU, received 7 days of treatment (i.e., maximum 14 doses), or died.  
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1 All co-interventions, such as phosphate replacement and nutrition (23),  
2 occurred as per standard care directed by the treating clinician.  
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## 8 **Outcomes**

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10 The primary outcome was arterial blood lactate. Arterial blood gases were  
11 recorded 6-hourly for 7 days in those with an arterial catheter. Given blood lactate was  
12 anticipated to trend to normal over time in all patients who survived, the predominant  
13 effect upon lactate was anticipated in the first 24 hours of treatment and so this epoch  
14 was identified as a co-primary outcome in addition to the 7 day study period.  
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## 26 ***Biochemical outcomes***

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28 Secondary biochemical outcomes including pH, blood glucose concentrations,  
29 glucose to lactate ratio, and serum phosphate and creatinine concentrations were  
30 recorded.  
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## 38 ***Co-administered interventions***

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40 Co-administered interventions such as enteral nutrition, calculated enteral  
41 thiamine, phosphate and insulin were recorded.  
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## 48 ***Clinical outcomes***

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50 The number of days of vasopressor therapy, censored at 7 days, was the major  
51 clinical outcome of interest. Patients who were not receiving vasopressor therapy at  
52 randomization were excluded from this analysis. Clinical outcomes included hospital  
53 mortality and number of days of admission censored at day 90.  
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3 **Statistical analyses**  
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6 Data are summarized as mean (standard deviation, SD), median [interquartile  
7 range, IQR] or difference (with 95% confidence intervals, CIs), with between-group  
8 differences reported by t-test, rank-sum test, or chi-squared test as indicated.  
9  
10 Differences in temporal profiles were assessed by generalized estimating equations  
11 regression, employing robust standard errors to allow for within-subject correlation,  
12 with between group differences reported as the mean with 95% CIs and plotted as the  
13 temporal mean profiles. Interaction effects between plasma lactate, glucose,  
14 phosphate and pH were explored by assignment group.  
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28 For the co-primary outcome, plasma lactate was analyzed as the absolute and  
29 relative change per hour from baseline, taken at 24 hours or when last measured in  
30 those with length of stay less than 24 hours. Between-group differences were analyzed  
31 by t-test and reported as the difference with corresponding P-values. Days of  
32 vasopressor therapy are reported both as the absolute number and as the proportion  
33 of study days received, with between group differences by rank-sum test. The  
34 significance level was set at 0.05 with no adjustment for multiple comparisons  
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48 Analysis were performed in Stata/MP 16.1®.  
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54 **Sample size**  
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57 The sample size was calculated using published data from Donnino and  
58 colleagues who reported blood lactate in patients with septic shock receiving thiamine  
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1 (27). Assuming that mean was equal to median and standard deviation equal to the  
2 interquartile range divided by 1.3, the difference in blood lactate at 24 hours between  
3 groups was estimated at 25%. Using Satterthwaite's t test for unequal variances, 72  
4 participants were required for a two-sided  $\alpha$  error of 0.05 and  $\beta$  error of 0.2 to detect a  
5 difference between groups of 25% or more, but to allow for dropouts and missing data  
6 the number of participants was inflated by  $\approx$  20% to 90 participants.  
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## 18 **RESULTS**

### 19 **Study participants**

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Between March 2019 and December 2020, 380 patients from five ICUs met all inclusion criteria with 90 patients meeting no exclusion criterion and randomized (Figure 1).

The study participants were well balanced in terms of baseline characteristics, pre-randomization treatments and biochemistry (Table 1 and Table S1, Supplementary Material). The majority of participants did not have risk factors on clinical history that would have identified a high risk of refeeding syndrome (Table 1).

### 66 **Study treatment**

At least 1 dose of exogenous thiamine was administered to every participant assigned to the intervention, and at no stage during ICU admission did a participant in the control group receive IV thiamine. The time from admission to randomization was similar between groups (median time from ICU admission to randomization, thiamine:

1 51 [35, 71] hours and control: 52 [42, 70] hours). Once randomized to the intervention  
2 group, participants received thiamine within 9 [1, 12] hours. Participants in the  
3  
4 intervention group received study treatment for a median of 11 [7.5, 13.5] doses with  
5  
6 mean IV administration of 371 [333, 400] mg/day for a mean total IV dose of 2200  
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8 [1500, 2700] mg of thiamine.  
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### 11 **Co-administered treatments**

12 The median [IQR] total days of enteral nutrition were similar between groups (thiamine:  
13  
14 6 [4, 7] vs. control: 5 [3, 7] days; P=0.22] as were volume of enteral nutrition (1041  
15  
16 [735, 1306] vs. 882 [777, 1164] mL/day; P=0.25), carbohydrates (144 [101, 185] vs.  
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18 119 [60, 158] g/day; P=0.06) and energy (1264 [893, 1632] vs. 1050 [525, 1395]  
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20 kcal/day; P=0.07).  
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31 The amount of enteral thiamine provided in nutrition formula was similar between  
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33 groups (12.1 [5.9, 15.1] vs 8.9 [4.6, 14.7] mg; P=0.23) but the total (IV + enteral) dose  
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35 of thiamine administered was substantially greater in the intervention group (2215  
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37 [1509, 2717] vs. 8.9 [4.6, 14.7] mg; **P<0.01**).  
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47 Phosphate administration was similar between groups (Table S2 and Figures S1 and  
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49 S2, Supplemental Material). A similar number of patients received insulin (20 (46%)  
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51 vs. 20 (44%); P=0.85) but the mean daily dose of insulin was substantially greater in  
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53 the intervention group (41 [19, 94] vs. 13 [3, 44] units/day; P=0.02).  
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3 **Primary Outcome**  
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6 The blood lactate concentrations over the 7-day time period were similar  
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8 between groups (1.2 (95% CI 1.1 to 1.3) mmol/L vs. 1.3 (1.1 to 1.4) mmol/L; difference  
9  
10 -0.1 (-0.2 to 0.1) mmol/L; P=0.55; Figure 2). There was no statistical difference in blood  
11  
12 lactate against time gradient in the first 24 hours (-0.02 (-0.03, -0.02) vs. -0.02 (-0.03,  
13  
14 -0.01) mmol/L/hour, P=0.32), nor in the relative change from baseline at 24 hours (-32  
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16 (-39, -26) vs. -24 (-31, -16) percent; P=0.09).  
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26 **Biochemical Outcomes**  
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29 Serum phosphate concentrations increased over time and were similar in both  
30  
31 groups (Figure S3, Supplemental Material). All other biochemical outcomes (pH,  
32  
33 glucose and creatinine) were similar between groups (Figures S4 –S6, Supplemental  
34  
35 Material)  
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42 **Clinical outcomes**  
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45 Days of vasopressor therapy was similar between groups (2 [1, 4] versus 2 [0,  
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47 5.5] days, P=0.37). Hospital mortality (9 (21%) vs. 5 (11%); P=0.25) and duration of  
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49 hospital admission were also not statistically different between groups (20 [11, 26] vs.  
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51 20 [11, 36] days; P=0.96)  
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## Subgroup analysis

To assess whether results were affected by relatively low blood lactate at randomization post hoc analyses were conducted. Inferences did not vary according to lactate at randomization ( $P=0.89$ ) or for those with a lactate  $> 2.0$  mmol/L at randomization ( $P=0.33$ ). There were insufficient numbers of patients with admission diagnosis of septic shock ( $n=5$ ) or severe hypophosphatemia at randomization ( $n=7$ ) to analyze.

## Adverse Events

There were no adverse events reported with the use of IV thiamine.

## DISCUSSION

The major observation from this trial is that the administration of IV thiamine to critically ill patients who developed hypophosphatemia during enteral nutrition administration did not result in detectable differences in blood lactate or any measured biochemical or clinical outcome.

Severe metabolic disturbances occur in patients with refeeding syndrome. Indeed, severe hypophosphatemia in patients with risk factors is considered the pathognomonic feature of the syndrome (28, 29). In patients with established refeeding syndrome, treatment with phosphate replacement, thiamine administration and calorie restriction is accepted as a standard of care (28). However, most episodes of hypophosphatemia associated with commencing enteral nutrition occur in patients

1 with no risk factors for, or additional clinical features of, refeeding syndrome (2, 4). The  
2 incretin hormone secretion secondary to enteral nutrient stimulates insulin secretion  
3 causing marked intracellular shift of phosphate, which requires exogenous  
4 supplementation of phosphate (30). In this trial, study participants had  
5 hypophosphatemia but none were identified by the treating clinical team as having the  
6 refeeding syndrome, with hypophosphatemia used as a biomarker to identify a cohort  
7 of patients who may be at risk of thiamine deficiency – with the assumption that  
8 pharmacological thiamine administration is more likely to benefit those who are  
9 deficient.  
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25 Whilst thiamine is reported by health care workers to be the most frequently  
26 administered vitamin in the ICU (7), there are only sparse data evaluating the efficacy  
27 of pharmacological thiamine administration during critical illness. Prior to the current  
28 study, the only randomized clinical trial that evaluated thiamine as a stand-alone  
29 treatment included 88 patients with sepsis from two ICUs (27). Administration of 200  
30 mg of thiamine twice daily was compared to usual care and, in the subgroup of patients  
31 who were subsequently identified as having thiamine-deficiency, the intervention  
32 reduced plasma lactate concentrations, improved renal function, and reduced  
33 mortality (27, 31). While results from this randomized clinical trial are supported by  
34 observations in cohort studies (17, 32) there is no current methodology to rapidly  
35 quantify plasma thiamine concentrations.  
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## 55 **Limitations**

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The major limitation of this trial was the open-label design. This was a pragmatic decision as the trial was only supported with seed funding and the cost of blinding an identifiable solution such as thiamine across multiple sites was prohibitive. Moreover, the primary outcome (blood lactate) is resistant to researcher bias. Nonetheless, the open label design increases the risk of investigators influencing results with confounding treatments. Co-interventions include nutritional therapy, which was not protocolized, and there is expert opinion that calorie restriction is beneficial in the acute phase of critical illness, particularly in patients who develop hypophosphatemia (22, 23, 33-36). However, there was greater, albeit not statistically significant, volume, carbohydrate and energy delivery in the group assigned to thiamine, which suggests that investigators and clinicians were not surreptitiously manipulating non-trial interventions to influence clinical outcomes. **Another co-intervention was phosphate administration. Whilst there were no statistical differences in phosphate administration (Table S2 and Figure S1) and plasma phosphate concentrations (Figure S3) between groups, an effect of thiamine, if one exists, may have been more apparent if phosphate administration had been restricted in both groups.**

This trial contained other limitations that should be acknowledged. Because of a lack of point-of-care testing to identify thiamine deficiency, this trial utilized a strategy of predictive enrichment with serum phosphate to identify a cohort that may benefit from thiamine administration (37). Whilst there is a biological rationale for this approach, **there is no established association between hypophosphataemia and thiamine deficiency. Moreover,** there was a trade off in terms of prognostic enrichment – i.e. an increased blood lactate was not an eligibility criterion. Accordingly, the current study did not evaluate whether patients with established thiamine deficiency and/or

1 increased blood lactate benefit from pharmacological administration of thiamine.  
2 Moreover, whilst there was no signal of patient-centered benefit with the intervention,  
3 these were only exploratory outcomes due to the small size of the cohort, and there  
4 may be important differences that were undetected. The sample size was based on a  
5 trial of patients in septic shock and was calculated to detect a between group  
6 difference in blood lactate of 25% or more. However, using these data for the sample  
7 size calculation for a trial of patients that did not have septic shock, risks missing a  
8 smaller but still clinically meaningful difference. Accordingly, this trial did not evaluate  
9 whether IV thiamine is a useful intervention in patients with septic shock and/or  
10 profound lactic acidosis (38, 39).  
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## 27 **Clinical impact**

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29 The implication for clinical practice is that thiamine supplementation does not  
30 appear to reduce blood lactate or be of substantial clinical benefit in this unselected  
31 sample population. Given the expense incurred with acquiring and administering  
32 thiamine, the use of thiamine should be limited to those suspected on clinical  
33 assessment to be at risk for thiamine deficiency or refeeding syndrome. Whether those  
34 at high risk of relative or absolute thiamine deficiency can be rapidly identified by other  
35 point of care techniques requires further evaluation (40).  
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## 51 **Conclusions**

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In critically ill enterally-fed patients who develop hypophosphatemia without prominent features of thiamine deficiency, the pharmacological administration of thiamine has no effect on blood lactate.

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## REFERENCES

1. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, et al: Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med* 2017; 43(3):380-398
2. Berger MM, Appelberg O, Reintam-Blaser A, Ichai C, et al: Prevalence of hypophosphatemia in the ICU - Results of an international one-day point prevalence survey. *Clin Nutr* 2020
3. Reintam Blaser A, Gunst J, Ichai C, Casaer MP, et al: Hypophosphatemia in critically ill adults and children - A systematic review. *Clin Nutr* 2020
4. Reintam Blaser A, van Zanten ARH: Electrolyte disorders during the initiation of nutrition therapy in the ICU. *Curr Opin Clin Nutr Metab Care* 2021; 24(2):151-158
5. Chapman M, Peake SL, Bellomo R, Davies A, et al: Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. *N Engl J Med* 2018; 379(19):1823-1834
6. Camp MA, Allon M: Severe hypophosphatemia in hospitalized patients. *Miner Electrolyte Metab* 1990; 16(6):365-368
7. Vankrunkelsven W, Gunst J, Amrein K, Bear DE, et al: Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: The VITA-TRACE survey. *Clin Nutr* 2021; 40(2):590-599
8. Moskowitz A, Donnino MW: Thiamine (vitamin B1) in septic shock: a targeted therapy. *J Thorac Dis* 2020; 12(Suppl 1):S78-S83
9. Donnino MW, Carney E, Cocchi MN, Barbash I, et al: Thiamine deficiency in critically ill patients with sepsis. *J Crit Care* 2010; 25(4):576-581
10. Costa NA, Gut AL, de Souza Dorna M, Pimentel JA, et al: Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. *J Crit Care* 2014; 29(2):249-252
11. van Snippenburg W, Reijnders MGJ, Hofhuis JGM, de Vos R, et al: Thiamine Levels During Intensive Insulin Therapy in Critically Ill Patients. *Journal of Intensive Care Medicine* 2017; 32(9):559-564
12. Gundogan K, Akbudak IH, Bulut K, Temel S, et al: Thiamin Status in Adults Receiving Chronic Diuretic Therapy Prior to Admission to a Medical Intensive Care Unit: A Pilot Study. *Nutr Clin Pract* 2019; 34(4):565-571
13. Berger MM, Manzanares W: Micronutrients early in critical illness, selective or generous, enteral or intravenous? *Curr Opin Clin Nutr Metab Care* 2021; 24(2):165-175
14. Fujii T, Deane AM, Nair P: Metabolic support in sepsis: corticosteroids and vitamins: the why, the when, the how. *Curr Opin Crit Care* 2020; 26(4):363-368
15. Collie JTB, Greaves RF, Jones OAH, Lam Q, et al: Vitamin B1 in critically ill patients: needs and challenges. *Clin Chem Lab Med* 2017; 55(11):1652-1668
16. Ridley EJ, Peake SL, Jarvis M, Deane AM, et al: Nutrition Therapy in Australia and New Zealand Intensive Care Units: An International Comparison Study. *JPEN J Parenter Enteral Nutr* 2018; 42(8):1349-1357
17. Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, et al: Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients With Septic Shock. *Crit Care Med* 2018; 46(11):1747-1752
18. Kaukonen KM, Bailey M, Egi M, Orford N, et al: Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. *Crit Care Med* 2014; 42(6):1379-1385

19. Hernandez G, Bellomo R, Bakker J: The ten pitfalls of lactate clearance in sepsis. *Intensive Care Medicine* 2019; 45(1):82-85
20. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, et al: Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37(5):1670-1677
21. Chebl RB, Tamim H, Dagher GA, Sadat M, et al: Serum Lactate as an Independent Predictor of In-Hospital Mortality in Intensive Care Patients. *J Intensive Care Med* 2020; 35(11):1257-1264
22. Olthof LE, Koekkoek W, van Setten C, Kars JCN, et al: Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. *Clin Nutr* 2018; 37(5):1609-1617
23. Doig GS, Simpson F, Heighes PT, Bellomo R, et al: Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med* 2015; 3(12):943-952
24. Boot R, Koekkoek K, van Zanten ARH: Refeeding syndrome: relevance for the critically ill patient. *Curr Opin Crit Care* 2018; 24(4):235-240
25. Reintam Blaser A, Rice TW, Deane AM: Update on nutritional assessment and therapy in critical care. *Curr Opin Crit Care* 2020; 26(2):197-204
26. Harris PA, Taylor R, Minor BL, Elliott V, et al: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
27. Donnino MW, Andersen LW, Chase M, Berg KM, et al: Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. *Crit Care Med* 2016; 44(2):360-367
28. McKnight CL, Newberry C, Sarav M, Martindale R, et al: Refeeding Syndrome in the Critically Ill: a Literature Review and Clinician's Guide. *Curr Gastroenterol Rep* 2019; 21(11):58
29. Ribeiro AC, Dock-Nascimento DB, Silva JM, Jr., Caporossi C, et al: Hypophosphatemia and risk of refeeding syndrome in critically ill patients before and after nutritional therapy. *Rev Assoc Med Bras (1992)* 2020; 66(9):1241-1246
30. Plummer MP, Hermanides J, Deane AM: Incretin Physiology and Pharmacology in the Intensive Care Unit. *Crit Care Clin* 2019; 35(2):341-355
31. Moskowitz A, Andersen LW, Cocchi MN, Karlsson M, et al: Thiamine as a Renal Protective Agent in Septic Shock. A Secondary Analysis of a Randomized, Double-Blind, Placebo-controlled Trial. *Ann Am Thorac Soc* 2017; 14(5):737-741
32. Holmberg MJ, Moskowitz A, Patel PV, Grossestreuer AV, et al: Thiamine in septic shock patients with alcohol use disorders: An observational pilot study. *J Crit Care* 2018; 43:61-64
33. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, et al: Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med* 2015; 372(25):2398-2408
34. Lheureux O, Preiser JC: Is slower advancement of enteral feeding superior to aggressive full feeding regimens in the early phase of critical illness. *Curr Opin Clin Nutr Metab Care* 2020; 23(2):121-126
35. van Zanten ARH, De Waele E, Wischmeyer PE: Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care* 2019; 23(1):368
36. Arabi YM, Al-Dorzi HM: Trophic or full nutritional support? *Curr Opin Crit Care* 2018; 24(4):262-268

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37. Wernerman J, Christopher KB, Annane D, Casaer MP, et al: Metabolic support in the critically ill: a consensus of 19. *Crit Care* 2019; 23(1):318
  38. Fujii T, Luethi N, Young PJ, Frei DR, et al: Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA* 2020; 323(5):423-431
  39. Sevransky JE, Rothman RE, Hager DN, Bernard GR, et al: Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA* 2021; 325(8):742-750
  40. Arabi YM, Casaer MP, Chapman M, Heyland DK, et al: The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017; 43(9):1239-1256

**Author contributions:**

1  
2 A.M.D was responsible for trial conceptualization, methodology, obtaining resources,  
3  
4 funding, conducting the trial, analysis and drafting the manuscript; A.J was responsible  
5  
6 for trial conceptualization, methodology, conducting the trial, analysis and critical  
7  
8 revision of the manuscript; B.T and A.C were responsible for conducting the trial,  
9  
10 project administration and critical revision of the manuscript; M.E.F was responsible  
11  
12 for trial conceptualization, methodology, funding, data resources, statistical analysis  
13  
14 and critical revision of the manuscript; J.T.C and M.J.M. were responsible for trial  
15  
16 conceptualization, methodology, funding and critical revision of the manuscript; R.G,  
17  
18 A.N and T.F. were responsible for trial conceptualization, methodology, conducting the  
19  
20 trial and critical revision of the manuscript ; K.B., J.S.D, A.A.U, M.Y, G.R, K.F. M.J.P,  
21  
22 F.Y were responsible for conducting the trial and critical revision of the manuscript;  
23  
24 and R.B and Y.A were responsible for trial conceptualization, methodology, obtaining  
25  
26 resources, funding, conducting the trial, analysis and critical revision of the manuscript.  
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**Figure 1.** CONSORT flow diagram

**Figure 2.** Mean plasma lactate levels, with 95% confidence intervals for the mean, by study group for days 1-7. Thiamine group shown as solid line and diamonds, control group as dashed line and open circles. The numbers of patients per group each day are shown above the x-axis, control above and thiamine below.

## Supplemental material

**Table S1. Additional demographic details by Randomization group**

IQR = interquartile range, APACHE = Acute Physiological and Chronic Health Evaluation, ICU = Intensive Care Unit

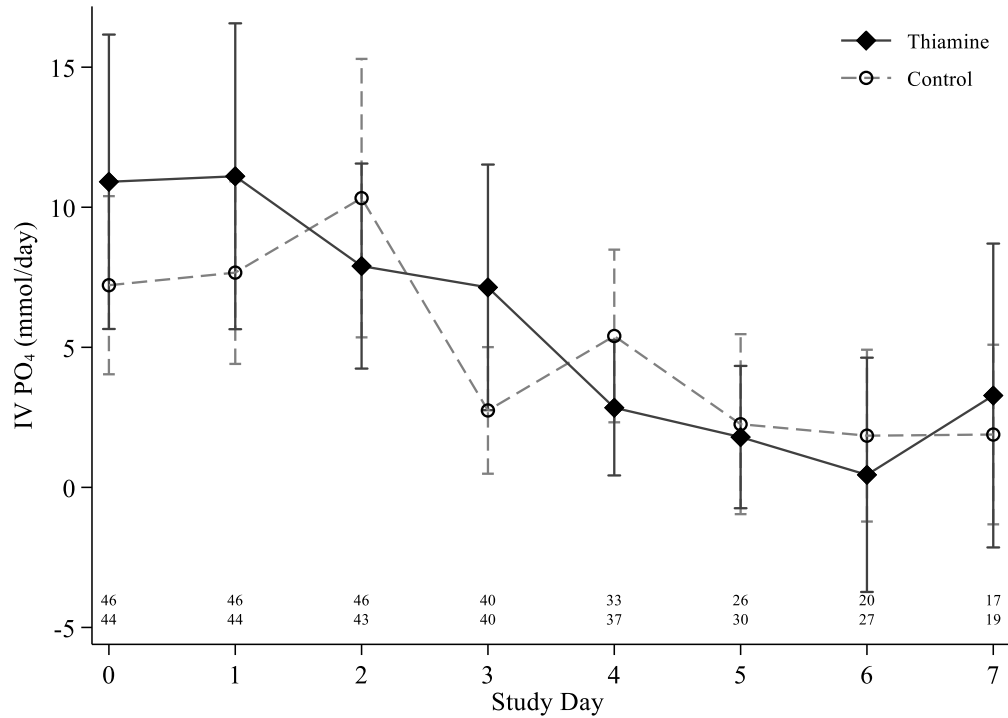
Variable	Thiamine n=44	Control n=46
APACHE-III Risk of Death (%), median [IQR]	14 [5, 42]	12 [4, 33]
Diagnostic Group, n (%)		
Trauma	16 (36)	21 (46)
Infective	7 (16)	5 (11)
Post-Cardiac Arrest	3 (6.8)	4 (8.7)
Cardiac Surgical	0 (0)	2 (4.3)
Cardiovascular	1 (2.3)	0 (0)
Neurosurgical	7 (16)	4 (8.7)
Neurology Medical	6 (14)	6 (13)
Other	4 (9.1)	4 (8.7)
ICU admission source, n (%)		
Emergency department	16 (36)	19 (41)
Ward	5 (11)	5 (11)
Operating room	21 (48)	20 (44)
Other hospital	2 (4.5)	2 (4.3)
ICU admission category, n (%)		
Elective surgery	2 (4.5)	1 (2.2)
Emergency surgery	20 (46)	20 (44)
Non-operative	22 (50)	25 (54)
Enteral Nutrition Hours (in ICU), median [IQR]	27 [19, 44]	30 [24, 46]
IV phosphate (within 24 hrs), n (%)	33/44 (75)	36/45 (80)
IV phosphate (mmol), median [IQR]	20 [20, 40]	20 [20, 35]
Insulin therapy (within 24 hrs), n (%)	14/44 (32)	14/45 (31)
Highest blood lactate mmol/L, median [IQR]	1.6 [1.3, 1.8]	1.2 [1.0, 2.1]
Baseline lactate $\geq$ 2 mmol/L, n (%)	10 (23)	13 (28)
Most recent pH < 7.3, n (%)	1 (2.3)	1 (2.2)
Most recent blood glucose mmol/L, median [IQR]	8.5 [7.7, 9.9]	7.9 [7.2, 9.3]
Most recent serum creatinine $\mu$ mol/L, median [IQR]	65 [54, 74]	68 [59, 89]

**Table S2. Concurrent therapies**

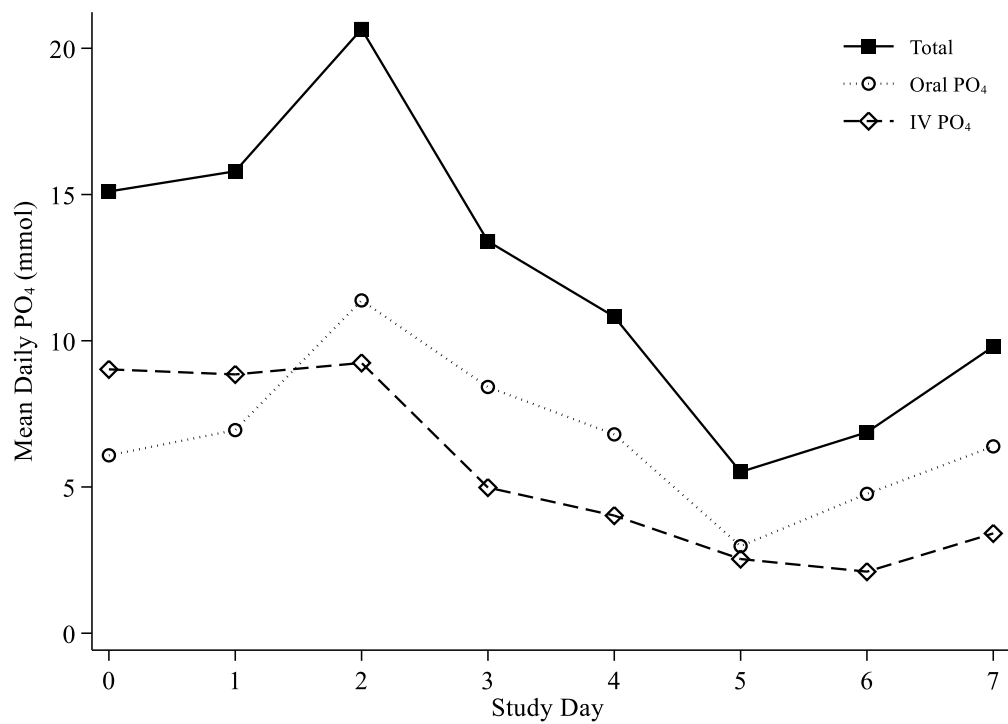
Administration of concurrent therapy	Thiamine Group n=44	Control Group n=46	p-Value
Phosphate Therapy			
IV therapy, n (%)	31 (71)	30 (65)	0.60
IV, mean mmol/day <sup>1</sup>	6.7 [3.3, 11.7]	6.7 [4.0, 10.0]	0.81
Oral therapy, n (%)	19 (43)	13 (28)	0.14
Oral, mean mmol/day <sup>1</sup>	13.4 [6.4, 24.2]	18.4 [8.1, 24.1]	0.74
Insulin Therapy <sup>1</sup> , units/day	41 [19, 94]	13 [3, 44]	0.02
Management - On Any ICU Day, n(%)			
Invasive mechanical ventilation	43 (98)	44 (96)	>0.99
Renal replacement therapy	5 (11)	7 (15)	0.76
Vasopressor(s)	31 (71)	40 (87)	0.06
Insulin	20 (46)	20 (44)	0.85
Invasive mechanical ventilation (days), median [IQR]	5 [3, 7]	4 [3, 7]	0.35
Insulin (Units/day) <sup>1</sup>	41 [19, 94]	13 [3, 44]	0.02

<sup>1</sup>Dose values are the mean value per patient over study days, summarized as the median [IQR] over study groups.

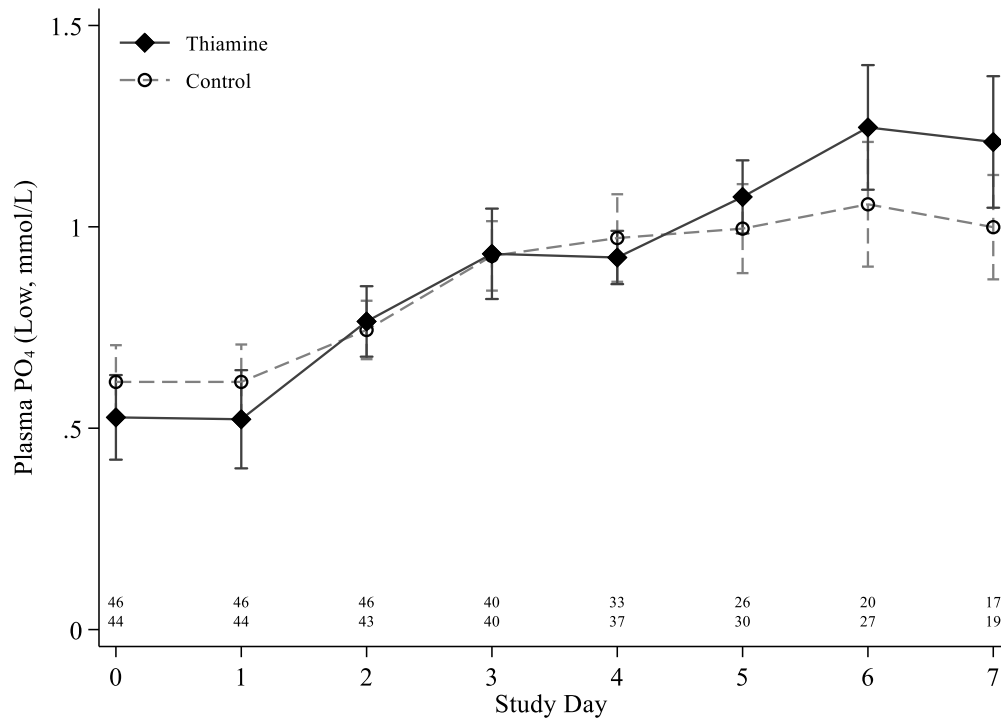
**Figure S1.** Mean IV phosphate administration, with 95% CI for mean, by study day and study group.



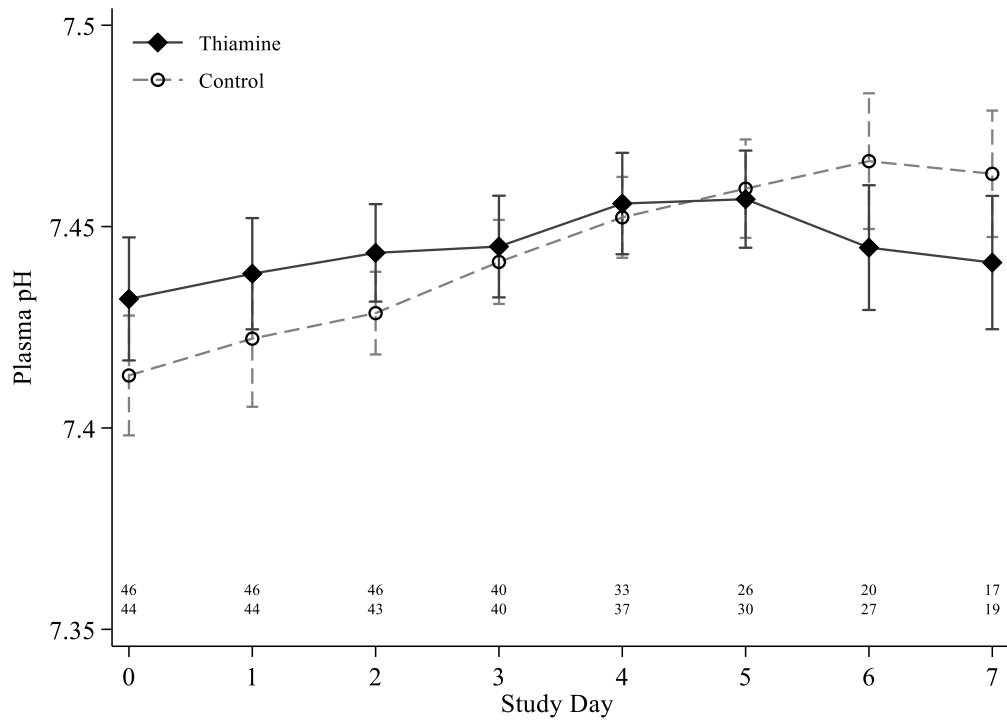
**Figure S2.** Administered supplemental phosphate, total and by route, by study day.



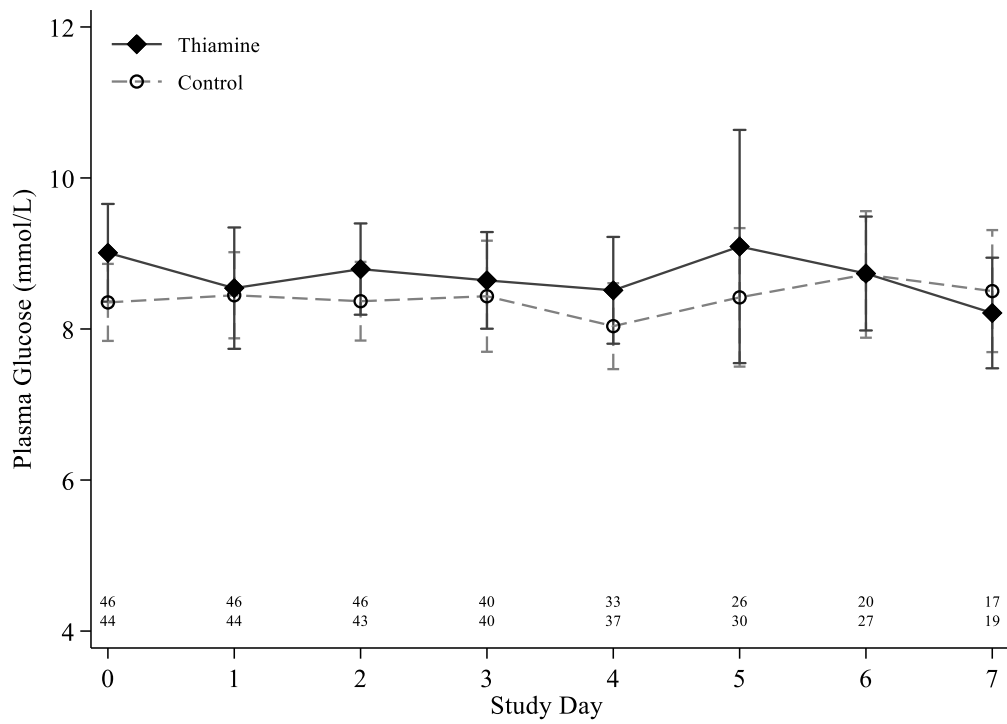
**Figure S3.** Mean lowest plasma phosphate, with 95% CI for mean, by study day and study group.



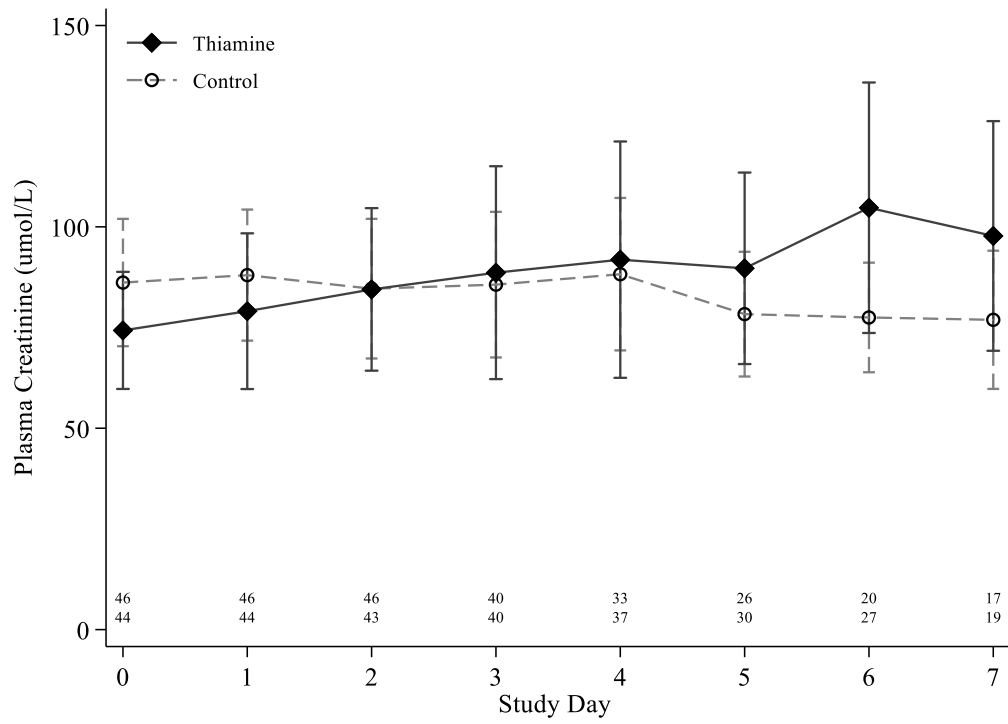
**Figure S4.** Mean plasma pH, with 95% CI for mean, by study day and study group.

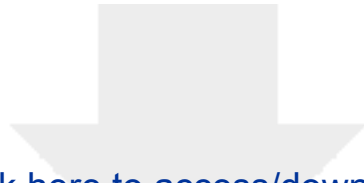


**Figure S5.** Mean plasma glucose concentration, with 95% CI for mean, by study day and study group.

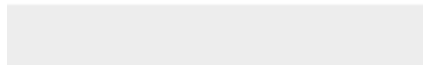


**Figure S6.** Mean plasma creatinine, with 95% CI for mean, by study day and study group.





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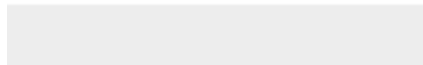
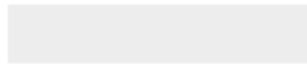




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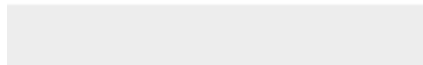
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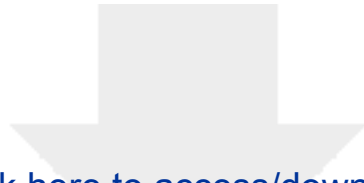
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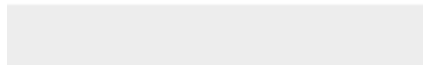


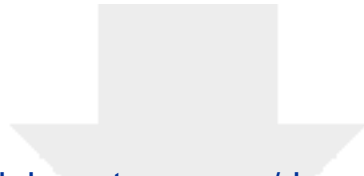
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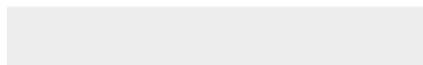


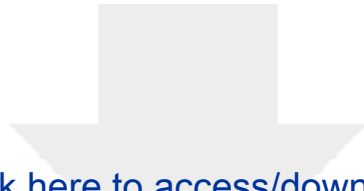
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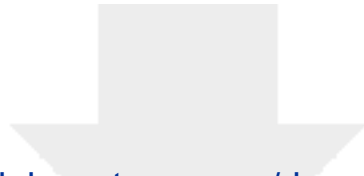


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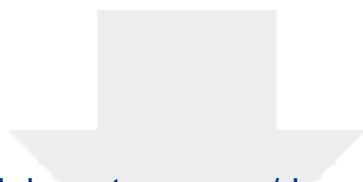
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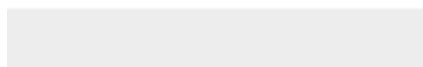
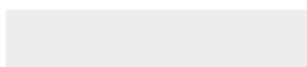


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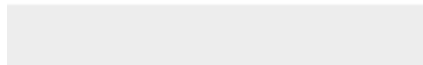


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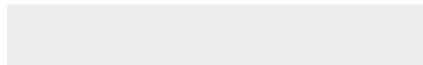


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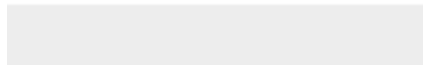


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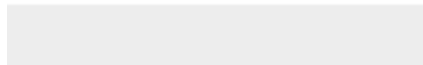
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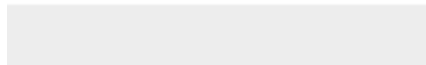


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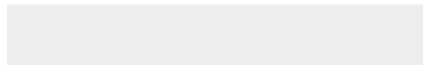


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