Title

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Journal

Journal of Parenteral and Enteral Nutrition, 40(6)

ISSN

0148-6071

Authors

Cvijanovich, Natalie Z
King, Janet C
Flori, Heidi R
et al.

Publication Date

2016-08-01

DOI

10.1177/0148607115572193

Peer reviewed

Published in final edited form as:

JPEN J Parenter Enteral Nutr. 2016 August ; 40(6): 860–868. doi:10.1177/0148607115572193.

A Safety and Dose-escalation Study of Intravenous Zinc Supplementation in Pediatric Critical Illness

Natalie Z. Cvijanovich, MD, FAAP[1], **Janet C. King, PhD**[2], **Heidi R. Flori, MD, FAAP**[1], **Ginny Gildengorin, PhD**[2], **Alexander A. Vinks, PharmD, PhD**[3,5], and **Hector R. Wong, MD**[4,5]

[1]Divisions of Critical Care at Children's Hospital and Research Center Oakland, Oakland, California

[2]Children's Hospital Oakland Research Institute, Oakland, California

[3]Division of Clinical Pharmacology, University of Cincinnati, Cincinnati, Ohio

[4]Division of Critical Care, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio

[5]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio

Abstract

Background—Critically ill children have low plasma zinc (pZn), correlating with organ failure. Since Zn influences inflammation, immune function, and glucose control, Zn supplementation is a plausible therapeutic modality. We sought to determine a safe dose of IV Zn to restore pZn in critically ill children.

Methods—Stepwise dose-escalation study of IV Zn supplementation at a tertiary children's hospital. All children (<10 years) admitted to PICU with PRISM III score > 5 OR ≥ one new organ failure were eligible. After consent, patients were sequentially enrolled into 4 dosing groups: 1) No zinc, 2) Zn250: 250 μg/kg/day ZnSO4, 3) Zn500: 500 μg/kg/day ZnSO4, or 4) Zn750: 750 μg/kg/day ZnSO4. ZnSO4 was administered 3 times daily for 7 days. pZn was measured at baseline, end of first ZnSO4 infusion, 1 hour post-infusion, and 7 hours post-infusion on Day 1, then daily trough Days 2–7. IL-6, CRP, and lymphocyte subsets were measured Days 1 and 3. Glucose was measured three times daily for 7 days.

Results—24 patients were enrolled. Baseline demographics were similar among groups. Baseline pZn was low in all patients (mean 41.8 μg/dL, standard deviation ± 16.0). pZn increased over the study period in supplemented groups; however, mean pZn in the Zn750 group exceeded 50th percentile. pZn was not associated with IL-6, CRP, or lymphocyte subsets among groups. Degree of hyperglycemia did not differ among groups. No patient had a study-related adverse event.

Conclusions—IV zinc supplementation at 500 μg/kg/day restores pZn to near 50th percentile and is well tolerated.

Address for correspondence: Natalie Z. Cvijanovich, Division of Critical Care, Children's Hospital and Research Center Oakland, 747 52nd Street, Oakland, CA 94609.

Keywords

Zinc; inflammation; lymphopenia; hyperglycemia; pediatrics; critical illness

Introduction

The association of low plasma zinc levels (pZn) with critical illness has become increasingly evident over the last several years, leading to a growing interest in investigating the potential therapeutic benefit of zinc supplementation[1–10]. The biologic functions of zinc are varied, but in the setting of critical illness its involvement in the maintenance of intact immune function as well as its role in glucose homeostasis may be particularly relevant. Since decreased pZn is associated with critical illness, and in one study lower pZn was associated with increased numbers of organ failures and measures of inflammation[11], it is plausible that zinc supplementation may mitigate the effects of injury and illness and the associated dysregulation of the immune system and stress hyperglycemia that result in significant morbidity and mortality. Zinc has therefore been a component of multiple trials of immune enhancing formulas or "cocktails" in immunomodulatory treatments[12]. To date, however, there has been no consistent demonstration of improvement in infection rates or mortality with this strategy.

Generally, supplemental zinc has been given orally in studies of children with diarrhea or pneumonia in developing countries, where pre-existing dietary zinc deficiency is common. A recent large, randomized, double-blind placebo controlled trial of oral zinc supplementation in 550 children 2–24 months old hospitalized with severe or very severe pneumonia showed no difference in time to recovery, though there was a trend toward more rapid recovery in the more severely ill group[13]. One of the reasons for this negative result may be that absorption via the oral route is impaired in the setting of critical illness[14]. Intravenous (IV) supplementation would eliminate this confounder; however, safety and dosing guidelines for IV zinc supplementation have not been established. We therefore completed a prospective phase I/II study of safety and pharmacokinetics of IV zinc supplementation in a population of critically ill children.

Materials and Methods

Setting and patients

This was a single center study performed in the pediatric intensive care unit (PICU) at Children's Hospital & Research Center Oakland (CHRCO); Clinicaltrials.gov NCT01062009. CHRCO is a 179 bed free-standing children's hospital, and the PICU is a 23 bed multidisciplinary unit that admits a broad spectrum of medical/surgical patients including patients who have undergone cardiac surgical procedures. Children admitted to the PICU from February 2009 to August 2012 were screened for study eligibility based on admission log and chart review.

Based on the pilot study that informed the current investigation[11], inclusion criteria were 1) age between 1 month and 10 years, 2) either unadjusted PRISM (Pediatric Risk of Mortality)

III score of greater than 5, as described by Pollock et al.[15], OR at least 1 new organ failure as described by Proulx et al.[16], and 3) anticipated PICU length of stay of > 3 days. Patients were excluded if 1) consent was not obtained, 2) they had known zinc deficiency (i.e., acrodermatits enterohepatica), 3) they had pre-existing bone marrow failure or a new or existing diagnosis of diabetes mellitus, 4) there were limitation of care orders in place or anticipated survival < 28 days, or 5) they had a clinical contraindication to zinc supplementation. After enrollment of the first three groups of patients, concern arose from review of existing literature that there may be potential harm with high dose zinc supplementation in the setting of neurologic injury[17–19], so an additional exclusion criterion of traumatic brain injury or new encephalopathy was added for enrollment in the high dose group. The Institutional Review Board at CHRCO approved the study, and all parents provided informed consent. Assent was waived due to the severity of illness of the eligible subjects. A Data Safety Monitoring Board was established that reviewed study results at the completion of enrollment of each study group.

Procedures

After consent was obtained, baseline demographic data were obtained. Study Day 0 was defined as the day of enrollment. In order to standardize administration times, zinc supplementation was started the following morning at 0800 (Study Day 1). Clinical data were recorded daily for 7 days. Because this was a safety and dose-finding pharmacokinetic study, patients were divided into four groups of six patients each, as determined by the pharmacokinetic modeling described below, with stepwise increase in zinc supplementation dose. The first (NoZn) group (6 patients) served as the control group and received no zinc supplementation, but serial pZn levels and all other study labs were performed as in the supplemented groups. Subsequent patients received zinc intravenously starting at 0800 on Day 1 through 2400 on Day 7, or until discharge if prior to 7 days, according the following progression: 1) the low dose (Zn250) group (6 patients) received 250 μg/kg/day of elemental zinc divided three times daily, 2) the medium dose (Zn500) group (6 patients) received 500 μg/kg/day of elemental zinc divided three times daily, and finally 3) the high dose (Zn750) group (6 patients) received 750 μg/kg/day of elemental zinc divided three times daily. Zinc was administered in the form of zinc sulfate (ZnSO4), initially at a concentration of 100 μg/mL in 0.9% NaCl, prepared by the research pharmacy at CHRCO. Due to the potential relatively large volume that concentration resulted in for larger patients, the protocol was amended after the first three patients were enrolled, with the concentration being changed to 200 μg/mL ZnSO4. All patients had central venous access and ZnSO4 was administered centrally over one hour.

Progression to testing the next higher dose in the subsequent group of patients was based on two *a priori* criteria: 1) if pZn of the supplemented group was not restored to at least the 50th percentile in 4 of the 6 patients, and 2) the safety profile was acceptable, i.e., no increased fever without clinical cause, no decrease in plasma copper (given the inverse relationship between zinc and copper), and no other unexpected adverse event potentially attributable to zinc supplementation. Results of each group were summarized and presented to the DSMB prior to proceeding with enrollment of the subsequent 6 patients into the next higher dosing group.

Blood samples were obtained from indwelling central venous or arterial catheters and were aliquoted for processing as follows: 1) 0.5 mL into heparinized metal-free tubes on ice for analysis of zinc and copper levels (determined by atomic absorption, Children's Hospital Oakland Research Institute); 2) 0.5 mL into EDTA tube for Luminex interleukin-6 (IL-6) assays (Luminex, Austin, TX); 3) 2 mL for serum chemistries, albumin, alkaline phosphatase, and C-reactive protein (CRP); and 4) 1 mL into EDTA tube for complete blood count with differential and lymphocyte subsets. Whole blood glucose was measured at the bedside with Nova Statstrip Glucose Meter (Nova Biomedical, Waltham, MA). Urine was collected for determination of urinary zinc:creatinine ratio.

In order to assess the potential effect of zinc on glucose homeostasis, we developed a glucose homeostasis score (GHOS) to take into account the degree of hyperglycemia as well as the need for insulin over the course of the 7 day study period. This score is an ordinal scale ranging from 1 to 5, with a score of 1 indicating no hyperglycemia, and 5 indicating severe hyperglycemia despite insulin administration. The GHOS scale is based on increasing levels of serum glucose, which correspond to the American Diabetes Association guidelines for the diagnosis of diabetes and impaired glucose tolerance[20]. In addition, the two highest glucose ranges in the GHOS scale have been correlated with increased mortality in critically ill children[21,22]. Patients were assigned a daily GHOS based on the highest measured glucose of the day, plus an additional point if they were on insulin (Table 1).

Treatment guidelines were not standardized and were left at the discretion of the clinical care team. Specifically, patients received standard amounts of zinc from parenteral or enteral nutrition regardless of study group. Total zinc intake was recorded for each patient during the study period.

Data analysis

Data analysis was conducted using SAS Version 9.3. Basic descriptive analyses of all demographic, clinical, and laboratory data were conducted on each of the four groups in the study. Pearson correlations were used to assess the correlations of zinc levels with IL-6 and CRP levels. For examining the associations of zinc, CRP, and IL-6 levels and ratios with the number of organ failures Spearman's correlation and the Mann-Whitney test were used.

Differences between groups at baseline and in each follow-up were investigated for all demographic outcome variables using the appropriate analysis of variance model (ANOVA) and chi square analyses. When necessary, non-parametric Kruskal-Wallis or Mann-Whitney tests were applied. The major hypotheses of group differences and changes over time were evaluated using general linear models for longitudinal data. The use of longitudinal models enabled us to account for within-patient correlations that were introduced in the data by the repeated measures across the study time-points. Models also adjusted for baseline differences when necessary. If significant differences were found between the groups, Tukey's method of multiple comparisons was used. A significance level of 0.05 was used for all statistical tests.

Pharmacokinetic analysis

A zinc pharmacokinetic profile was determined for each individual patient at the start of treatment on Day 1. Based on results of our previously published pilot study of pZn in 20 critically ill patients, a sample size of six patients in each group was determined to be adequate for pharmacokinetic parameter estimation. Samples for pharmacokinetic analysis were drawn according to a sparse D-optimal sampling strategy[23]. In addition, to allow estimation of zinc exposure during therapy six pre-dose (trough) samples were drawn at 24, 48, 72, 84, 96 and 106 hours into therapy. Plasma concentration-time data were explored graphically and by compartmental analysis with the software package MW/Pharm (Version 3.6, Mediware, Groningen, the Netherlands)[24,25]. Pharmacokinetic (PK) analysis was performed using a Bayesian PK model-based approach with a zinc population model adapted from the literature using allometric scaling[26–28]. Post hoc Bayesian parameter estimates were generated for zinc total body clearance, volume of distribution and half-life. The PK model was also used to evaluate predicted zinc concentration-time profiles as part of the dose escalation study.

Results

During the study period, 24 patients were enrolled, with 6 patients enrolled in each group sequentially. The baseline demographic characteristics are shown in Table 2. The underlying diagnoses were varied, as expected, and included sepsis in 4, pneumonia (viral or bacterial) in 8, trauma (including traumatic brain injury) in 5, repair of congenital heart disease in 2, intestinal volvulus in 2, and encephalitis, intracranial hemorrhage, and hydrocarbon inhalation each in one child. All patients completed the study, and no patients died during the study. There were no differences in baseline demographics among the four groups of patients.

Zinc

All patients had low pZn on Day 1 of ICU admission (41.8 μg/dL ± 16.0) (mean ± SD) compared with normal reference ranges. The 50th percentile range of normal pZn in children < 10 years old is 75–80 μg/dL and the 2.5th percentile is 56–57 μg/dL. There was no difference found in baseline pZn among groups (p=0.44). Whereas the NoZn (control) group showed no increase in pZn over the 7 day study period (p=0.54), pZn increased significantly from Day 1 to Day 7 in all three zinc supplemented groups (Zn250, p=0.01; Zn500, p=0.03; Zn750, p<0.0001 comparing Day 1 to Day 7). Furthermore, among the three zinc supplemented groups, pZn increased more rapidly as the dose increased (Figure 1A). In the Zn750 group, pZn levels reached the 50th percentile by Day 7 of supplementation (mean 93.3 μg/dL; SD ± 8.75). Plasma copper levels increased slightly with time in all three zinc supplemented groups, p=0.03 (Figure 1B), but remained within normal limits.

Zinc and intermediate outcomes

Over the seven day period of zinc supplementation, PELOD[29] scores decreased in all groups, but there was no difference in scores among groups. All patients had at least one organ failure on the day of enrollment, and organ failure tended to resolve by Day 7, though

because of the small number of patients in each group, statistical significance could not be tested.

The correlations between pZn and IL-6 or CRP on Day 1 were not significant (Zn and IL-6, r = −0.39, p = 0.06; Zn and CRP, r = −0.32, p = 0.14). There was no difference in interleukin-6 (IL-6) on Day 1 across dosing groups, nor was there a significant change in IL-6 with time among groups. The NoZn group had significantly lower Day 1 C-reactive protein (CRP) levels than the Zn750 group (p=0.02), but there was no significant difference in the change in CRP over all time points (p=0.30) (see Table 3). There was no difference in urinary excretion of zinc between or among groups over all time points, p=0.12 (data not shown). There was also no difference in lymphocyte numbers, distribution of lymphocyte subsets on Day 1 or Day 3 of PICU admission, or change in lymphocyte subsets over time among the four groups (Table 3).

The Zn750 group tended to have lower median GHOS scores, but there was no difference in median GHOS between the controls and the zinc supplemented groups at all time points (p=0.08) (Figure 2).

Zinc dosing

Plasma zinc pharmacokinetics were calculated for each patient based on the Day 1 profile as well as the subsequent daily trough levels. A sample graph from a patient in each supplemented group is provided for illustration (Figure 3). In aggregate, mean clearance was 5.77 ± 2.57 mL/hr/kg, volume of distribution was 1.39 ± 0.46 L/kg, and $T_{1/2}$ (half life) was 181.36 ± 56.29 hours. Based on pharmacokinetic modeling, the 500 μg/kg/day IV zinc supplementation dose nearly restored levels to within the normal range, without inducing prolonged periods of pZn above normal.

Safety

The zinc infusion appeared to be well tolerated by all children. Early in the study it was the subjective impression of the nursing staff that the infusion may cause some degree of phlebitis when infused peripherally, so subsequent infusions were given centrally. All children in the study had central venous access. Potential safety concerns determined prior to the study included fever, anemia, and decreased copper levels. Given the inclusion criteria of critical illness as determined by PRISM score and organ failure, the study population was expected to have some degree of fever and anemia as a function of illness severity. There was no significant difference in the onset of new fever among study groups (p=0.24). Copper levels were not affected by zinc supplementation (Figure 1B). There were no adverse events related to the study. One infant with respiratory syncytial virus (RSV) sepsis developed refractory hypoxemia and required cannulation for ECMO (extracorporeal membrane oxygenation) on study Day 6, but this event was reviewed by the DSMB and determined to be unrelated to the study. No children died, and there was no negative effect attributable to zinc supplementation.

Discussion

This is the first study of intravenous (IV) zinc supplementation in critically ill children. Consistent with previous studies of zinc in critically ill children[11,30], pZn was low at baseline and increased over the 7-day study period. Importantly, IV zinc was well tolerated in all dosing groups. All of the children in the 750 μg/kg/day group achieved normal plasma zinc levels, but four of the six children in that group had supra-therapeutic levels of plasma zinc (>120 μg/dL). There did not appear to be toxicity associated with this, but given the small number of patients in the group we cannot conclude that 750 μg/kg/day is safe. Although we do not yet have evidence of a beneficial physiologic effect of any of the doses in this pilot/safety study, based on the pharmacologic data demonstrating restoration toward normal without exceeding the upper range of normal, we concluded that 500 mcg/kg/day is a well-tolerated dose of IV zinc supplementation in critically ill children, and is a reasonable starting point for a randomized, controlled, multicenter trial to evaluate the safety, efficacy, and clinical benefit of this intervention.

In recent years there has been a paradigm shift in the concept of nutrition as a therapeutic modality, specifically the use of micronutrients as “pharmaconutrients” to positively impact outcomes in critical illness. There has been growing interest in administration of micronutrients for anti-oxidant effect, anti-inflammatory properties, and immunomodulation[2–5,7–10,31–39]. Some common components of these “cocktails” have included glutamine, arginine, omega-3 fatty acids, selenium, and zinc. Unfortunately, studies have often combined several of these micronutrients in one patient population. This method runs the risk of masking a potential beneficial, or harmful, effect of a single component of the cocktail. In a recently published large, randomized study of supplementation of critically ill children with glutamine, selenium, zinc and metoclopramide[9], no benefit of the combination of pharmaconutrients was demonstrated, though in a subgroup of immunocompromised patients there was a lower incidence of healthcare associated infection. Since then, a large trial of glutamine and anti-oxidant supplementation in critically ill adults showed an *increase* in mortality among the glutamine-supplemented group, and no improvement in outcomes among patients supplemented with an anti-oxidant combination comprised of selenium, zinc, beta carotene, Vitamin E and Vitamin C[35]. Thus it is imperative to evaluate micronutrients individually to the extent possible in order to determine effects specific to that micronutrient.

The association of decreased plasma zinc levels with acute illness has been demonstrated in multiple studies[11,40–43]. The exact mechanism by which this occurs, and the benefit or detriment of this response is not clear. In a study of genomic responses of children with SIRS/sepsis, decreased plasma zinc levels were associated with non-survival in the setting of septic shock[44]. A subsequent pilot study of 20 critically ill children presenting with a wide range of diagnoses demonstrated that decreased plasma Zn levels correlated with degree of organ failure[11]. It is important to note that these decreased plasma Zn levels are not a true zinc deficiency, but are rather, at least in part, a reflection of the body’s response to illness or injury. It has been shown that in acute illness, Zn is redistributed from the serum to other tissues[45]. One of the most important mechanisms for this redistribution is induction of hepatic metallothioneins, which are cysteine-rich intracellular metal binding proteins

important in the homeostasis of essential metals and participants in the acute inflammatory response. Levels of hepatic metallothioneins increase rapidly in response to cytokine release associated with inflammation or injury, quickly sequestering plasma zinc into the liver for the synthesis of acute phase proteins essential to the stress response[45,46]. Furthermore, this stress response results in acutely increased urinary Zn excretion[40,47–49], decreasing total body zinc stores. A temporary decrease in plasma Zn may be beneficial in limiting the cytokine response during inflammation[45]. Since zinc is a trace element required by all organisms, including bacteria and fungi, one can postulate that low plasma zinc levels might in part be a protective host response, limiting availability of zinc to bacteria, analogous to the acute drop in iron levels in the setting of sepsis[50,51]. There is, however, no evidence to support this theory, and in fact a recent study by Eijkelkamp et al.[52] described a mechanism for a potential toxic effect of extracellular zinc on *S. pneumoniae*. It is unlikely, therefore, that zinc supplementation would be harmful, but this question clearly requires further investigation.

This study was a pilot/safety study and as such was not powered to evaluate efficacy of IV zinc supplementation, but outcome variables reflected potential areas of benefit. Zinc is known to be required for normal function of the immune system, has anti-inflammatory properties, and is required for insulin function and glucose homeostasis. It has been well established that pZn is low in the setting of critical illness[9,11,41], and the degree of relative hypozincemia correlates with organ failure[9,11]. Zinc supplementation has the potential to positively impact morbidity and perhaps mortality associated with critical illness, but until now there have not been established guidelines for dosing, pharmacokinetics or safety profile to inform a large-scale, randomized, placebo-controlled efficacy trial of IV zinc supplementation. We chose to evaluate markers of inflammation (IL-6 and CRP), immunodeficiency/immunoparalysis (lymphocyte subsets), and glucose homeostasis in order to model such a large scale trial, but without the intent to determine efficacy based on these parameters.

Although enteral zinc supplementation has been studied extensively both in the developing world[7,8,53–55], where dietary zinc deficiency is relatively common, as well as in some populations of critically ill patients[3,4,6,9,35,56,57], there have been very few studies of parenteral zinc supplementation, with the majority having been done in populations known to have increased zinc losses, such as burn patients[3,4,58,59], and none in pediatrics. Parenteral zinc is thought to be safe and is routinely used in parenteral nutrition preparations. There are no reports of toxicity from IV zinc in physiologic doses, and doses as high as 900 mcg/kg/day have been well tolerated[60]. Two case reports of accidental significant parenteral zinc overdose describe fever and anemia[61,62]. In this study we had no evidence of toxicity among the supplemented patients.

There was concern that copper levels would be affected by zinc supplementation. Although the most significant interaction between zinc and copper administration occurs when these trace elements are given enterally, there is some evidence that there may be post-absorptive interactions between copper and zinc with regard to modulation of metallothionein expression, with concomitant alteration in metal concentrations[63]. With this potential concern in mind, since copper levels were included in the measurement of trace element

levels and did not require additional blood sampling, we elected to analyze them to ensure that there was no evidence of a significant interaction. However, we found no decrease in plasma copper with zinc supplementation.

Limitations of the study include the small sample size in each group, with multiple comparisons. The study population was quite varied in age and diagnosis, and it is possible that zinc supplementation would have differing effects in more homogeneous diagnostic subgroups of patients. However, for the purposes of this phase I/II study, and based on the pilot study of zinc homeostasis in critically ill children, the authors felt that this diversity provides generalizability for future studies. Secondly, measurement of plasma zinc does not reflect the total body zinc status of a patient, and therefore a patient with low pZn may not have true zinc deficiency. However, since previous work has shown a correlation between pZn and organ failure[11], and furthermore there is currently no “gold standard” measurement of zinc status, in order to minimize phlebotomy and obtain pharmacokinetic and pharmacodynamic measurements we elected to use pZn as our outcome measure. Finally, the compensatory anti-inflammatory response syndrome (CARS) associated with critical illness and initial systemic inflammatory response is generally recognized to occur 7–10 days after the initial insult, so measurement of inflammatory markers and lymphocyte subsets on Day 3 were likely premature. However, given the small number of patients in each group and the short average length of stay of PICU patients in general, we felt that waiting until Day 7 of supplementation would result in loss of data points.

Conclusion

Low plasma zinc levels are prevalent among critically ill children and are associated with the degree of organ failure. Intravenous zinc supplementation is a biologically plausible therapeutic modality, but until now safety and appropriate dosing has not been established. Based on this dose-escalation study, IV zinc supplementation is well-tolerated, and a dose of 500 μg/kg/day restores plasma zinc levels to near the 50th percentile of normal values without exceeding normal concentrations. A multi-center, randomized, controlled trial of IV zinc supplementation to study its effect on inflammation, immunity, and glucose homeostasis is warranted.

Acknowledgments

This work was supported in part by an intramural grant from Children’s Hospital and Research Center Oakland and by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Clinical Relevancy Statement

Zinc status influences multiple aspects of the host response to stress from illness or trauma, and low plasma zinc concentrations are associated with critical illness. Zinc supplementation presents a potential therapeutic intervention to improve morbidity and mortality associated with critical illness. This study is the first to assess the safety and appropriate dosing of IV zinc in critically ill children. The results will inform a multicenter randomized clinical trial of zinc supplementation to assess its efficacy in improving immune function and glycemic control.

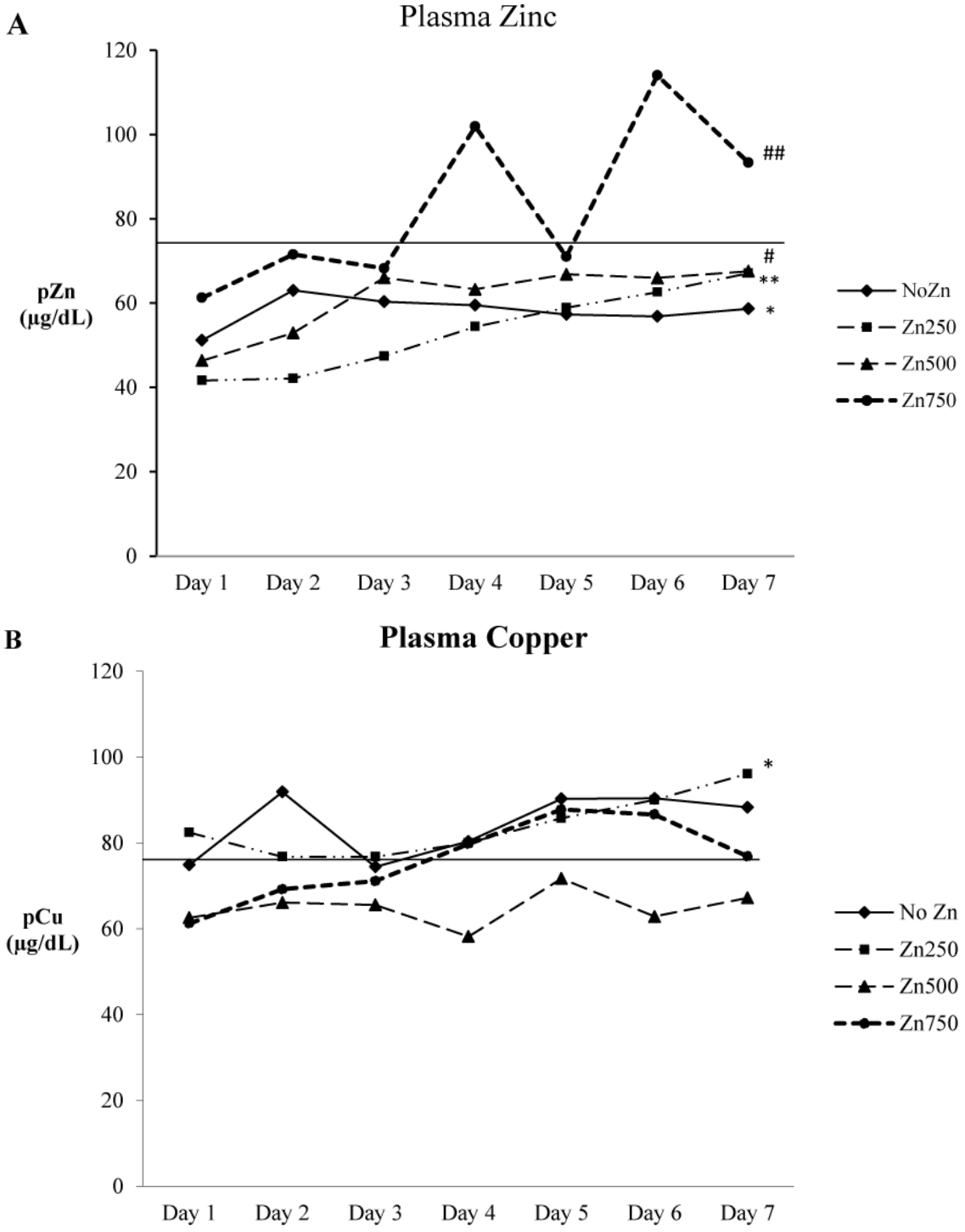

Figure 1.

Mean plasma Zn and Cu concentrations over time. **A**. Plasma zinc (pZn) concentration by group. Single horizontal line represents 50th percentile (75 µg/dL) Day 1 to Day 7 change: *No Zn, p=0.54; **Zn250, p=0.01; $^{\#}$Zn500, p=0.03; $^{\#\#}$Zn750, p<0.001 **B.** Plasma copper (pCu) concentration by group. Single horizontal line represents 50th percentile (65 µg/dL). Day 1 to Day 7 change *p=0.03; **NS=not significant

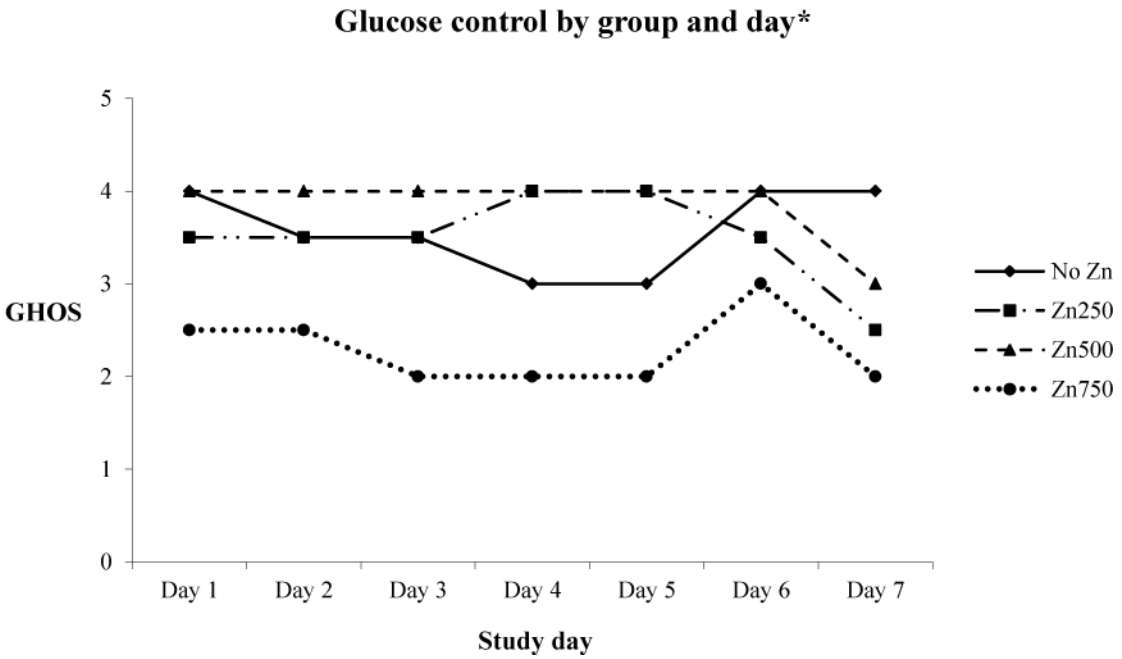

Figure 2.

Median daily glucose homeostasis score (GHOS) by study group. Higher number indicates greater degree of hyperglycemia. *p=0.08 for change in score among groups

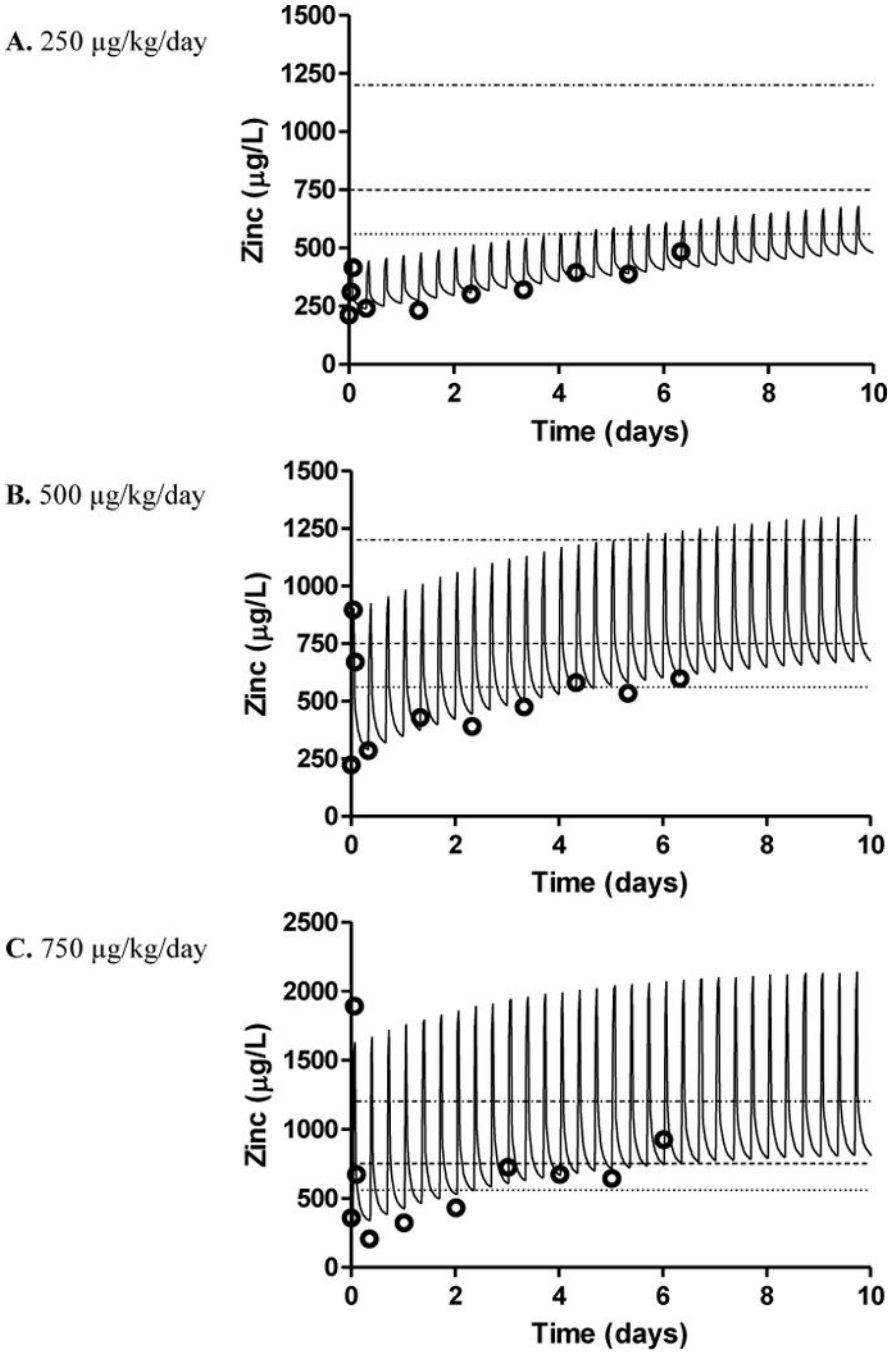

Figure 3.

Pharmacokinetic profiles of a representative patient from each supplemented study group. Dashed horizontal lines represent 2.5th, 50th, and 97.5th percentile [pZn]. Open circles represent specific time points of measurement. **A.** Zn250 patient; **B.** Zn 500 patient; **C.** Zn750 patient. **Note**: Scale in **C** has been widened to optimize graph

Table 1

Glucose homeostasis score (GHOS)

Maximum daily glucose (mg/dL)	Points*
<100	1
100–125	2
126–140	3
>140	4

* Insulin infusion adds 1 point to the maximum score

Table 2

Patient characteristics

Characteristic	NoZn (N=6)	Zn250 (N=6)	Zn500 (N=6)	Zn750 (N=6)	p value
Age (years; median, IQR)	1.5 (0.6–4.8)	1.8 (0.8–2.8)	5.3 (1.9–6.4)	2.8 (0.8–5.2)	0.59
Gender					0.72
Male	33% (2)	50% (3)	33% (2)	50% (3)	
Female	67% (4)	50% (3)	67% (4)	50% (3)	
Severity of illness					
PRISM III (median, IQR)	12 (5–17)	8 (3–16)	12 (6–19)	9 (7–10)	0.92
PIM (median, IQR)	3.4 (1.6–17.1)	6.0 (4.2–7.2)	7.0 (4.0–23.0)	5.2 (2.8–7.8)	0.47
PELOD (median)	11 (4–11)	11 (4–19)	20 (13–21)	21 (14–21)	0.23
No of pts with ≥ 2 organs failed	50% (3)	50% (3)	67% (4)	50% (3)	0.88
Length of stay (days; median, IQR)					
PICU	8 (8–11)	8 (5.75–18.5)	18.5 (10.8–26.25)	10.5 (8.5–11.75)	0.61
Hospital	10 (8.25–16.25)	12 (8.75–28.75)	25.5 (15.8–33.75)	16 (13.5–20.75)	0.47

JPEN J Parenter Enteral Nutr. Author manuscript; available in PMC 2017 September 22.

Table 3

Lymphocyte subsets and inflammatory markers

	No Zn		Zn250		Zn500		Zn750		p-value
	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	
Lymphocytes (mean ± SD)									
Total T %	65.8 (7.2)	67.8 (13.3)	60.0 (9.3)	63.2 (17.0)	62.7 (11.1)	67.7 (12.1)	61.0 (15.6)	66.8 (18.1)	NS *
CD4 %	42.4 (6.8)	43.8 (16.9)	35.0 (5.8)	40.0 (16.3)	39.5 (12.1)	44.5 (11.8)	41.8 (15.0)	48.8 (18.8)	NS
CD8 %	22.0 (7.6)	18.8 (4.4)	22.2 (11.0)	21.0 (10.1)	20.5 (4.9)	21.2 (5.2)	17.2 (3.6)	17.2 (6.3)	NS
CD19 %	29.4 (6.5)	23.3 (6.1)	35.2 (10.0)	31.2 (14.8)	33.7 (9.9)	28.8 (12.4)	34.6 (12.6)	28.3 (15.5)	NS
NK %	3.4 (2.3)	7.3 (7.8)	3.4 (2.4)	3.3 (2.4)	2.2 (2.0)	1.8 (0.8)	3.8 (3.7)	3.8 (3.7)	NS
CD4/CD8 ratio	2.12 (0.85)	2.7 (1.5)	2.1 (1.4)	2.5 (2.1)	2.1 (0.9)	2.2 (0.9)	2.5 (1.1)	3.2 (1.7)	NS
Inflammatory markers (median, IQR)									
IL-6 (pg/mL)	50.5 (19.8–78.3)	11.5 (6.5–17.3)	76.0 (20.3–137.0)	39.0 (37.0–84.0)	22.4 (15.1–103.8)	20.0 (8.8–112.2)	168.9 (107.1–287.4)	19.5 (12.0–25.0)	0.078 **
CRP (mg/dL)	5.6 (3.1–7.2)	1.5 (1.1–3.0)	10.4 (6.3–16.0)	7.6 (4.4–17.5)	10.0 (5.7–16.1)	5.4 (3.8–8.3)	25.8 (17.0–35.4)	15.5 (9.2–17.6)	0.301 **

* NS = not significant ($p > 0.05$)

** No difference in change in IL-6 or CRP from Day 1 to Day 3 among groups

IL-6, interleukin 6; CRP, C-reactive protein, IQR, interquartile range, SD, standard deviation