

Selenium in Early Sepsis: A Marker for Change?

W Graham Carlos, MD, Curtis Ramsey MS, and Joseph Fraiz, MD

St Vincent Hospital and Health Systems, Indianapolis, IN, USA

Sepsis is the leading cause of mortality in the critically ill. Recent studies emphasize early classification and treatment as paramount to improving mortality rates. Biomarkers are gaining interest as a means to accurately assess and prognosticate septic patients. This prospective, observational study examined the role of selenium (Se) as a biomarker in sepsis. Se is a trace element that is vital to the functioning of the intracellular enzyme glutathione peroxidase (GPX) thus serving an important role in the modulation of oxidative stress that occurs in sepsis. Previous studies of patients with severe oxidative stress have demonstrated decreases in GPX activity. We examined the role of assessing serial Se concentrations in 30 septic patients upon admission to the intensive care unit and found statistically significant correlations between trends in Se concentrations and clinical course. *Adv Sepsis* 2008;6(3):99–102.

The role that selenium (Se) plays in reducing the oxidative stress response observed in critical illness and sepsis has been under increasing investigation worldwide over the past several years. In an analysis of 21 healthy subjects, Harrison and colleagues demonstrated that plasma Se is distributed in three major Se-containing proteins: selenoprotein-P ($52\pm 6\%$), glutathione peroxidase (GPX; $39\pm 6\%$), and albumin ($9\pm 4\%$) [1]. When combined with GPX, Se serves as a free radical scavenger and performs an important role in reducing oxidative damage [2]. In 1990, Hawker and colleagues found that decreased plasma Se concentrations are common in intensive care unit (ICU) patients [3]. In 1998, Forceville demonstrated that the plasma Se concentration was negatively correlated to sepsis severity in 40 out of 134 medical and surgical patients assayed upon ICU admission. In addition, they found that patients with low plasma Se concentrations on ICU admission had higher rates of nosocomial pneumonia, organ system failure, and mortality compared with other ICU patients [4]. Not surprisingly, studies examining Se supplementation began to appear shortly thereafter.

In 2004, the first Cochrane meta-analysis on Se supplementation was published [5]. It included seven randomized trials involving a total of 813 patients, and concluded that there was insufficient evidence to recommend Se supplementation in critically ill patients; however, the quality of the included trials as reported was poor. In contrast, a meta-

analysis in 2005 showed an association between decreased mortality rates and Se supplementation [6]. In 2007, Sakr and colleagues studied 60 predominantly post-surgical patients of whom 15 were diagnosed with severe sepsis ($n=3$) or septic shock ($n=12$). They found an association between low plasma Se concentrations and organ dysfunction, tissue damage, infection, and mortality in the ICU [7]. During the same year, two other studies looking at Se administration in septic patients were published. Angstwurm et al. performed a prospective, randomized, placebo-controlled, multicenter study in patients with systematic inflammatory response syndrome (SIRS), sepsis, and septic shock, which revealed that adjuvant treatment of patients with high-dose sodium-selenite resulted in a 14.3% absolute reduction in mortality rate at 28 days [8]. Forceville conducted a multicenter, randomized, double-blind study comparing administration of sodium-selenite versus placebo in severe septic shock patients with documented infection and did not find statistically significant differences in mortality rates between the two groups at any time point [9].

Clearly, the evidence for the association with depleted plasma Se concentrations and organ dysfunction secondary to sepsis continues to grow, sparking these recent therapeutic trials. This is in spite of a lack of knowledge regarding the etiology of the association. Elucidating the trafficking of Se amongst plasma proteins and selenoenzymes during oxidative stress would contribute significantly to this knowledge gap.

Clinicians and researchers have called for improved precision in both clinical staging and prognosticating sepsis patients in an attempt to better time treatment modalities.

Address for correspondence: W Graham Carlos, St Vincent Hospital and Health Systems, Indianapolis, IN, USA. Email: gcarlos9@yahoo.com

In 2001, the International Sepsis Definitions Conference introduced the PIRO classification scheme to stratify patients on the basis of their: Predisposing conditions, extent of Infection, host Response, and Organ dysfunction. The aim of this system is to serve as a hypothesis-generating model for future research and it highlights the need for new sepsis biomarkers [10]. These studies, coupled with the need for new biomarkers to further define the response to sepsis, led us to the question of whether plasma Se concentrations could be helpful in staging and prognosticating septic patients, given the associations with sepsis and organ dysfunction, as previously demonstrated. Therefore, we aimed to examine Se concentrations at different levels of clinical staging as defined by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) classification system [11].

Methods

Thirty patients who were admitted to the ICU at St Vincent Hospital (Indianapolis, IN, USA) between December 2006 and July 2007, and diagnosed with sepsis, severe sepsis, or septic shock, as defined by the ACCP/SCCM classification system, were enrolled. Septic shock was defined as hypotension requiring vasopressor refractory to fluid challenge unexplained by other causes. Other required inclusion criteria were the documented presence of an infectious process such as: positive bacterial culture, pyuria, imaging evidence of abscess, vegetation, or pneumonia with purulent sputum, clinical evidence of cellulitis, gangrene, or wound infection. Every attempt was made to enroll patients consecutively; however, a 12-h enrollment window of ICU admission precluded the inclusion of a few patients. Patients were considered resolved when they no longer met SIRS criteria and were considered improved when they transitioned from sepsis to resolved, or septic shock to sepsis or resolved. Exclusion criteria included: limitation of care, end-phase chronic disease, patients on dialysis, pregnancy, active gastrointestinal bleeding, status post-cardiopulmonary resuscitation, or an episode of sepsis within the preceding 6 months. Written informed consent was obtained for each enrolled patient.

Following enrollment, a Simplified Acute Physiology System II (SAPS II) score was calculated using routine physiological measurements [12]. The following parameters were collected: age, sex, etiology of sepsis, sepsis stage, net fluids in and out, and method of nutrition. When these parameters could not be collected in real-time, the information was gathered retrospectively from the medical record of the patient. Early goal-directed therapy was initiated on all patients at the time of ICU admission consistent with our hospital sepsis bundle protocol. Data

Table 1. Mean Se concentrations by clinical stage at ICU admission.

Clinical stage	n	Se level ($\mu\text{g/L}$) \pm SD	95% CI
Sepsis	15	92.4 \pm 29.2	76.24, 108.56
Severe sepsis	8	97.1 \pm 20.3	80.15, 114.1
Septic Shock	7	78.7 \pm 18.5	61.62, 95.81

CI: confidence interval; ICU: intensive care unit; n: number of patients; SD: standard deviation; Se: selenium.

were collected at four separate timepoints beginning at enrollment (time 0), and then at 6 h, 18 h, and at the time of ICU discharge. Blood samples were collected from previously inserted central venous catheters at similar timepoints and the frozen specimens were sent to Quest Diagnostic Laboratories (CA, USA). The blood was tested for plasma Se concentration by inductively coupled-mass spectrometry (ICP-MS). Results were reported in $\mu\text{g/L}$ (conversion to $\mu\text{mol/L}$ = 0.0127). All statistical analyses were performed using SAS statistical software, SAS Institute Inc., Cary, NC, USA. Mean Se levels were compared using the Student's t-test.

Results

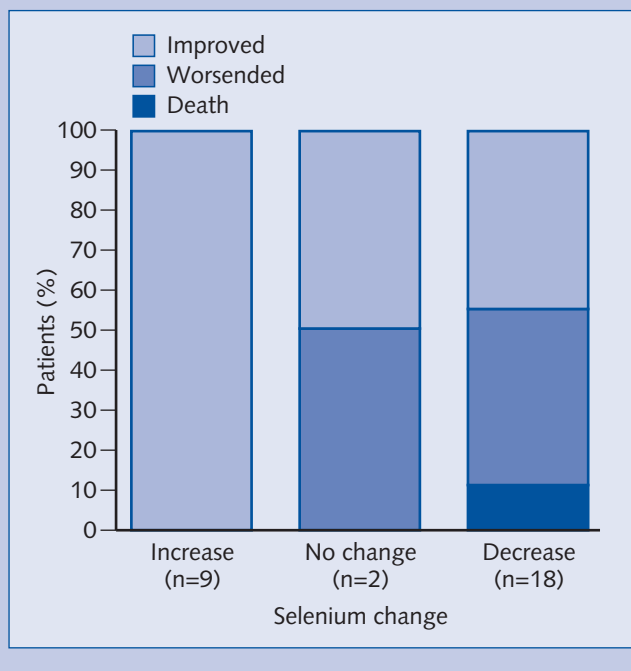
Among the 30 enrolled patients (13 female, 17 male), the mean age was 62 years (standard deviation [SD] 15.4 years) and the mean length of stay in the ICU was 6.03 days (interquartile range 4.25). Mortality rate for all enrolled patients was 7%. Patient diagnoses included: pneumonia (13 patients), urosepsis (nine patients), intra-abdominal infection (four patients), cellulitis (two patients), and surgical-site infection (two patients). Mean admission SAPS II scores for each clinical stage were as follows: sepsis 38, severe sepsis 42, and septic shock 53. Mean Se levels by clinical stage at hospital admission are shown in Table 1.

From time baseline (time 0) until 6 h, nine patients' Se concentrations increased, 18 decreased, two were unchanged, and one patient was lost to follow-up. No patient whose Se concentration increased from baseline progressed to severe sepsis or shock and all eventually resolved. Of the 18 patients with Se concentrations that decreased: three out of eight admitted with sepsis progressed to shock, all five patients admitted with severe sepsis progressed to shock, and two out of five patients admitted with shock died. Differences in net fluid calculations were not statistically significant ($p=0.28$). No patients received supplemental Se during the time 0–6-h or time 6–18-h intervals. There were statistically significant differences in mean Se concentrations between patients that

Table 2. Correlation of Se concentrations with clinical course.

0–6 h clinical course	Change Se concentration (mean) $\mu\text{g/L}$	SD	95% CI	p value
Improved (n=6)	3.67	8.26	-5.00, 12.34	0.0029
Worsened (n=7)	-16.71	10.66	-26.57, -6.86	
6–18 h clinical course				
Improved (n=10)	2.80	8.72	-3.44, 9.03	0.0009
Worsened (n=7)	-17.71	11.93	-28.74, -6.68	

CI: confidence interval; SD: standard deviation; Se: selenium.

Figure 1. Overall clinical course based on change in selenium concentration (0–6 h) during sepsis.

clinically improved versus those who worsened within 0–6 and 6–18 h, as shown in Table 2. A decline in Se concentrations was indicative of a worse prognosis as visualized in Fig. 1. From baseline to 18 h, there were 11 patients whose Se concentrations increased compared with 17 patients in whom Se concentrations decreased (one patient died before time 18 h and one specimen was lost). All 11 patients whose Se concentration increased survived to hospital discharge without further clinical deterioration. Mean Se concentrations at 6 h and 18 h after enrollment are listed in Table 3 by clinical stage determined concomitantly.

At the time of discharge from the ICU, one patient continued to meet criteria for sepsis. The remaining 29 patients had resolved or were deceased. The mean Se concentration of the 17 resolved patients at time of ICU discharge was 107 $\mu\text{g/L}$ with a standard deviation of

Table 3. Mean Se concentrations by clinical stage measured at 6 h and 18 h.

Clinical stage*	n**	Se concentration ($\mu\text{g/L}$)	SD
Time 6 h			
Sepsis	11	88.5	37.2
Severe Sepsis	4	84.8	34.3
Septic Shock	10	81.3	15.5
Resolved	4	96.0	27.9
Time 18 h			
Sepsis	10	96.0	29.4
Septic Shock	10	81.7	31.6
Resolved	7	88.7	27.3
Deceased	1	N/A	N/A

n: number of patients; N/A: not applicable; SD: standard deviation; Se: selenium.

*Clinical stage determined at 6 h and 18 h after enrollment.

**Two samples were lost.

29.7 $\mu\text{g/L}$ (some samples were lost or not drawn at the time of discharge). Two patients died from complications of sepsis (at approximately 8 h and 24 h). All surviving patients were receiving nutrition at the time of discharge; however, no patients received supplemental nutrition during the first 18 h of ICU admission.

Study limitations

Our study has several limitations. The first limitation was its small sample size. We were unable to confirm previous findings of significantly decreased Se concentrations upon ICU admission in patients presenting with septic shock [4], although we observed a similar trend. Our study was also limited by our inability to secure consecutive enrollment, thus making it susceptible to selection bias. Our reported mortality rate of 7% is lower than would be expected for this patient population. We attribute this, in part, to the low reserve for ICU transfer in our hospital for patients meeting

sepsis criteria, aggressiveness of early goal-directed therapy, and small sample size. While we measured plasma Se concentrations rather than whole blood levels, it has been previously shown that the concentration of Se in plasma is approximately 80% of that in whole blood [13]. Finally, the inability to secure all of our specimens, particularly at the latter timepoints, prohibited our ability to derive conclusions at time 18 h and discharge.

Discussion

The sepsis cascade remains one of the deadliest syndromes in critically ill patients worldwide. It is difficult to diagnose, stratify, and consequently to provide timely treatment interventions. Early, intensive monitoring with goal-directed therapy have demonstrated benefit [14], as has timely treatment with activated protein C (drotrecogin alfa [activated]) for severe sepsis [15]. Recognizing which patients are most likely to deteriorate would accelerate treatment interventions and likely improve outcomes. The aim of this study was to evaluate Se as a potential early sepsis biomarker by assessing serial Se concentrations. We did not track multiple organ dysfunction scores (MODS) or compare Se concentrations with other documented sepsis biomarkers such as C-reactive protein (CRP) or procalcitonin (PCT) but these would undoubtedly be useful in future studies. Of note, associations between minimum plasma Se concentration and leukocyte count, CRP, PCT, and interleukin-6 have previously been demonstrated [7].

This study involved a single hospital in the mid-western United States. Many of the previous studies have come from European countries with lower Se concentrations compared with the US on account of a low soil Se content and poor plant uptake [16]. For example, the Third Nutrition and Health Examination Survey (NHANES III) revealed that in the US the median serum Se concentration was 124 $\mu\text{g/L}$ [17], which is significantly greater than the current recommended range for optimizing activity of plasma GPX which is maximized at plasma concentrations of 70–90 $\mu\text{g/mL}$.

Our study demonstrated a trend towards decreased Se concentrations in patients presenting to the ICU in septic shock that was similar to the trend Forceville and colleagues observed in 1998 [4]. While we did not compare the study group to healthy controls, our Se concentrations upon ICU admission were much lower than those observed in the NHANES III population group. This finding is consistent with that of previous investigators who have demonstrated reduced Se concentrations upon ICU admission.

An important finding in this study was a statistically significant association between the absolute change in Se concentration within the first 18 h and clinical course, albeit we did not specifically track organ failures. We may only

speculate at the physiological explanation for this at the present time. Is early mobilization of Se protective against oxidative stress? Does early depletion of Se in sepsis indicate increasing oxidative stress and impending circulatory and perfusion abnormalities? Irrespective of the underlying etiology, additional studies are needed to further delineate the role of Se as a prognostic factor in sepsis. While the application of Se as a clinical tool would necessitate the development of a rapid bioassay such as has been developed for serum lactate concentrations, development of such a tool should not preclude further research.

In conclusion, early assessment of Se concentration trends may serve as a prognosticator of clinical deterioration in septic patients. Statistically significant correlations between sepsis course and change in Se concentration were observed, supporting the theory that Se may serve as a potential biomarker in sepsis and justifying further studies.

Disclosures

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References

- Harrison I, Littlejohn D, Fell G. Distribution of selenium in human blood plasma and serum. *Analyst* 1996;**121**:189–94.
- Macdonald J, Galley H, Webster N. Oxidative stress and gene expression in sepsis. *Br J Anaesth* 2003;**90**:221–32.
- Hawker F, Stewart P, Snitch P. Effects of acute illness on selenium homeostasis. *Crit Care Med* 1990;**18**:442–6.
- Forceville X, Vitoux D, Gauzit R et al. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med* 1998;**26**:1536–44.
- Avenell A, Noble DW, Barr J et al. Selenium supplementation for critically ill adults. *Cochrane Database Syst Rev* 2004;(4):CD003703.
- Heyland DK, Dhaliwal R, Suchner U et al. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med* 2005;**31**:327–37.
- Sakr Y, Reinhart K, Bloos F et al. Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multiorgan failure. *Br J Anaesth* 2007;**98**:775–84.
- Angstwurm M, Englemann L, Zimmermann T et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007;**35**:118–26.
- Forceville X. Effects of high doses of selenium, as sodium selenite, in septic shock patients: a placebo-controlled, randomized, double-blind, multi-center Phase II study – selenium and sepsis. *J Trace Elem Med Biol* 2007;**21**(Suppl 1):62–5.
- Levy M, Fink M, Marshall J et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250–6.
- American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;**20**:864–74.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;**270**:2957–63.
- Combs G Jr. Selenium in global food systems. *Br J Nutr* 2001;**85**:517–47.
- Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77.
- Bernard G, Vincent J, Laterre P et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699–709.
- Rayman M. The importance of selenium to human health. *Lancet* 2000;**356**:233–41.
- National Center for Health Statistics. National Health and Nutrition Examination Survey. Hyattsville, MD: National Center for Health Statistics. <http://www.cdc.gov/nchs/nhanes.htm>.