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Impact of the Nationwide Intravenous Selenium Product Shortage on the Development of Selenium Deficiency in Infants Dependent on Long-Term Parenteral Nutrition

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Abstract

Background: For patients dependent on parenteral nutrition (PN), selenium must be supplemented intravenously. A nationwide intravenous selenium shortage began in April 2011. The impact of this shortage on PN-dependent infants was evaluated by examining the provision of selenium, development of biochemical deficiency, and costs associated with the shortage. *Materials and Methods:* This single-center, retrospective study included PN-dependent infants aged ≤1 year who weighed ≤30 kg, received PN for ≥1 month, and had ≥1 serum selenium measurement. The primary outcome was the incidence of biochemical selenium deficiency. Secondary outcomes included severity of biochemical deficiency, clinical manifestations, costs, and relationship between serum selenium levels and selenium dose. *Results:* The average selenium dose decreased 2-fold during the shortage (2.1 ± 1.2 µg/kg/d; range, 0.2–4.6 µg/kg/d) versus the nonshortage period (3.8 ± 1 µg/kg/d; range, 2.4–6 µg/kg/d; $P < .001$). A linear relationship between serum selenium concentration and selenium dose was observed ($r^2 = 0.42$), with a dose of 6 µg/kg/d expected to result in normal serum levels in most cases. Similar proportions of patients developed biochemical deficiency in both groups: shortage period, 59.1%; nonshortage, 66.7%; $P = .13$. The severity of biochemical deficiency was similar between groups. A significant increase in incremental cost during the shortage was observed. *Conclusion:* This is the first study examining the impact of the intravenous selenium shortage on PN-dependent infants. Both groups exhibited similarly high incidences of biochemical selenium deficiency, suggesting higher empiric doses may benefit this population. However, ongoing shortages limit the ability to provide supplementation. (*JPEN J Parenter Enteral Nutr*. 2016;40:851-859)

Keywords

selenium; shortage; pediatric; parenteral nutrition; deficiency

Clinical Relevancy Statement

Nutrition-related product shortages remain an ongoing problem; however, the clinical impact of these shortages, especially on infants dependent on parenteral nutrition (PN), has not been clearly elucidated to date. Selenium is an essential trace element that plays important roles in thyroid function, growth and development, and immune function, and is critical to protect the cardiac myocytes against oxidative stress. This single-center, retrospective study evaluates the clinical impact of the intravenous selenium shortage on infants dependent on PN and the financial impact of the shortage and describes a linear relationship between intravenous selenium dose provided and serum selenium concentrations.

Introduction

Selenium, 1 of the 5 essential trace elements, plays important roles in thyroid function, growth and development, and immune function.[1-10] In addition, selenium is a critical component of glutathione peroxidases, and its antioxidant properties are particularly protective against oxidative stress in cardiac myocytes.[1,2,11-13] Dietary enteral intake is typically the main source of selenium[1,4-6,9-11]; however, for those unable to fulfill selenium requirements via the enteral route due to dependence on parenteral nutrition (PN), selenium must be supplemented intravenously. Current guidelines recommend providing intravenous selenium as part of the PN regimen at doses of 20–60 µg/d for adult patients, 40–60 µg/d for adolescents, and 1–2 µg/kg/d for infants and children.[5,6,11,14-16] Empiric doses of 3 µg/kg/d for PN-dependent neonates, infants, and pediatric patients may be provided, as data have indicated that 2 µg/kg/d may be inadequate to maintain normal selenium levels in these populations, with higher requirements dependent on clinical condition.[1,6,17] Intravenous selenium requirements have been suggested to be as high as 4.5 µg/kg/d for surgical neonates.[17,18]

The development of selenium deficiency is rare but may occur when intake is suboptimal over extended periods.[4,8,19,20] Occurrence is linked to poor diet, malabsorption syndromes, and dependence on long-term PN.[4,9,20,21] In adults, selenium deficiency is known to occur when intake is <30 µg/d for periods of time as short as 1 month.[4,8,9,19,20] In the pediatric

population, the dose at which selenium deficiency is most likely to occur is less well described. Infants and children may be at an increased risk of developing deficiency, as they do not have established reserves of selenium, and selenium requirements are higher per kilogram of body weight due to rapid growth and development.[1,16,22] Furthermore, most placental selenium transfer occurs after the 36th week of gestation, suggesting that preterm infants may be born with existing deficits.[17,18]

Clinical signs and symptoms of severe selenium deficiency include cardiomyopathy (manifested as heart failure and arrhythmias); hypothyroidism; mental and growth retardation; skin, hair, and nail effects; osteoarthropathy; hemolysis; and impaired cellular immunity.[4-6,11,19,21,23,24] The diagnosis of selenium deficiency is complex, involving both objective measurement of selenium status and clinical signs and symptoms of deficiency. Multiple selenium biomarkers are available, including plasma selenium levels, plasma glutathione peroxidases, erythrocyte selenium, erythrocyte glutathione peroxidases, selenoprotein P, whole-blood selenium, urinary selenium, and hair and nail selenium.[1,5,8,11,22,25] At present, the evaluation of serum selenium levels is the most clinically practical measurement available to assess biochemical selenium status.[1,5,8,11,22,25]

A national shortage of intravenous selenium began in April 2011, with no projected timeline to complete restoration of supply as of September 2014.[26,27] To cope with the shortage, the American Society for Parenteral and Enteral Nutrition provided recommendations, which include the use of enteral supplementation when possible, prioritization of supplies for vulnerable populations, and decreasing or eliminating the use of trace element additives in PN.[23,26,28] Because of the unavailability of single-ingredient intravenous selenium, at our institution the shortage was managed through various mechanisms, including prioritizing product to pediatric patients, decreasing doses or completely eliminating selenium from PN solutions, and using externally compounded selenium products or diluted adult multitrace-5 products, depending on availability.

Importantly, the clinical impact of the selenium shortage was recently described by Davis et al.[29] Five pediatric patients with intestinal failure were observed to have experienced severe biochemical selenium deficiency during the shortage period, highlighting the gravity of the shortage and its influence on patient outcomes. However, the impact of the intravenous selenium shortage on PN-dependent infants has not been described to date. Furthermore, the impact of such shortages on healthcare workers and health systems has not been fully measured. Therefore, this single-center, retrospective study was aimed at evaluating the clinical impact of the national intravenous selenium product shortage on the incidence of selenium deficiency in infants dependent on PN, as well as the financial impact of the shortage.

Methods

This single-center, retrospective study was conducted in accordance with the ethical standards set forth and approved by the Institutional Review Board at our institution. The study period included data from PN-dependent infants treated between August 1, 2010, and July 31, 2012. Patients were eligible for inclusion if they were ≤1 year of age at the time of study, weighed ≤30 kg, received long-term PN (defined as administration for ≥1 month), and had ≥1 serum selenium measurement during the study period. PN at our institution is ordered in 3 ways: <10 kg (neonatal/pediatric), 10–30 kg (neonatal/pediatric), and >30 kg (adolescent/adult). The weight cutoff of ≤30 kg was used to capture patients during

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the neonatal and infant periods. Included patients may have received PN in the hospital, in the home, or in both settings. Patients who exclusively received oral selenium supplementation and were not on PN were excluded from the study. No exclusions were made on the basis of gender, race, or diagnosis. Two groups of patients were identified: (1) those who received PN during the nonshortage period (August 1, 2010, to July 31, 2011) and (2) those who received PN during the shortage period (August 1, 2011, to July 31, 2012). The subset of patients who received PN during a period of time that overlapped both time periods was excluded from the primary analysis but included in secondary analyses.

For patients treated in the hospital setting, during periods of adequate intravenous selenium supplies (ie, nonshortage period, defined as the period spanning August 1, 2010, to July 31, 2011), a standard dose of 3 μg/kg/d could be added to PN solutions, with the ability to titrate to a maximum dose of 9 μg/kg/d based on selenium status. Baseline doses of 3 μg/kg/d were added and titrated to maintain serum selenium levels within the normal range, as past experience at our institution has shown that infants require higher doses to achieve normal levels. During periods of inadequate supply (ie, shortage period, from August 1, 2011, to July 31, 2012), the standard dose of selenium was initially reduced to 2 μg/kg/d while supplies of the single-ingredient intravenous selenium product lasted, and conservation efforts prioritized the remaining supply to neonates and infants, whereas older children and adult patients received limited to no selenium during the shortage period. When the single-ingredient intravenous selenium product supply was depleted (November 18, 2011), patients were transitioned to an adult multitrace element concentrate–5 product at a 10-fold dilution, which provided a selenium dose of 1.2 μg/kg/d. When supplies of this product were completely exhausted, selenium was eliminated from the PN solution altogether. This complete depletion of product occurred intermittently throughout the shortage period, because of variable product availability. Other than restricting supplies to neonates and infants, no additional prioritization (eg, serum selenium levels) for provision of selenium was made during the shortage period. In both the nonshortage and shortage periods, when supplies were available, selenium was dosed daily in the inpatient setting. Children receiving home PN provided by the home infusion pharmacy affiliated with our institution had intermittent access to intravenous selenium products during the shortage period, even when commercial products were unavailable, because of the use of an external compounding pharmacy. The compounding pharmacy strictly adhered to all United States Pharmacopoeia 797 guidelines. In addition to precise sterility and accuracy of production, the product also underwent outside stability, endotoxin, and sterility testing prior to distribution for patient use. All vials were stored frozen for up to 45 days until being distributed for patient use. However, supplies of these compounded products were inconsistent, and doses were variable. Therefore, for patients receiving home PN, doses could range from 3–9 μg/kg/d before the national shortage, and from 0–9 μg/kg/d during the national shortage. (Of note, because of the latest ruling by the Food and Drug Administration [FDA] on the regulation of outside pharmacies, the company has since stopped providing such products.) During the nonshortage and shortage periods, when supplies were available, selenium was dosed daily in the home setting. Throughout the study period, in both the inpatient and outpatient settings, selenium doses were adjusted for weight to account for growth.

All data were collected retrospectively and included mother demographics and characteristics, patient demographics (gender, race, gestational age at delivery, birth weight, delivery mode), growth parameters (height, weight, and head circumference), daily selenium dose (μg/kg/d), serum selenium concentrations (ng/mL; Mayo Clinic/Mayo Medical Laboratories), and clinical markers of selenium deficiency, including C-reactive protein levels, thyroid function tests (thyroid-stimulating hormone, thyroxine, and triiodothyronine), iron studies (hemoglobin, hematocrit, mean corpuscular volume, transferrin saturation, red blood cell distribution width, and ferritin), number of blood transfusions, and echocardiogram results.

The primary outcome measure was the incidence of biochemical selenium deficiency, defined as a serum selenium level below the lower limit of normal for age. Secondary outcome measures included severity of biochemical deficiency, the cost associated with management of the intravenous selenium shortage, clinical manifestations of deficiency, and the relationship between serum selenium concentrations with dose provided.

Statistical Analysis

All eligible study participants were included in the statistical analyses. Baseline descriptive statistics for patient characteristics measured as continuous variables were displayed as mean, standard deviation, and range; categorical variables were displayed as number and percentage. Comparisons of continuous baseline variables between subjects in the shortage period versus nonshortage period used an independent-samples *t* test for variables that were approximately normally distributed and a nonparametric Wilcoxon rank-sum test for nonnormally distributed variables. Categorical variables were compared between the shortage and nonshortage period using Pearson χ^2 test or Fisher exact test when the expected values were small. Comparison of the number of selenium levels measured for the nonshortage and shortage periods was made using a Poisson regression, which is appropriate for count data, with an offset for the number of months on PN for each infant, to control for time on PN in the analysis. Whether an infant was ever deficient or not was also modeled using a Poisson regression, controlling for the exposure time to PN for each child. The relationship between intravenous selenium dose provided in the previous 7 days and serum selenium concentration was analyzed using a linear mixed model, with a random effect for

Table 1. Baseline Patient Characteristics.

Variable	Shortage Period (n = 22)	Nonshortage Period (n = 15)	*P* Value
Gender, n (%)			.55
Female	11 (50)	6 (40)	
Male	11 (50)	9 (60)	
Race, n (%)			.38
Caucasian	17 (77.3)	9 (60)	
African American	4 (18.2)	3 (20)	
Other	1 (4.5)	3 (20)	
Delivery mode, n (%)			>.99
Vaginal delivery	8 (36.4)	6 (40)	
Cesarean delivery	12 (54.5)	9 (60)	
Unknown	2 (9.1)	0	
Primary diagnosis, n (%)			.31
Necrotizing enterocolitis	5 (22.7)	5 (33.3)	
Gastroschisis	3 (13.6)	5 (33.3)	
Short bowel syndrome	0	1 (6.7)	
Congenital diaphragmatic hernia	1 (4.5)	2 (13.3)	
Congenital cardiac abnormality	4 (18.2)	0	
Atresia	1 (4.5)	1 (6.7)	
Diarrhea/enterocolitis	1 (4.5)	1 (6.7)	
Malabsorption	2 (9.1)	0	
Hirschsprung disease	1 (4.5)	0	
Feeding difficulty	2 (9.1)	0	
Polycystic kidney	2 (9.1)	0	
Birth weight, g			.38
Mean ± SD	2299.6 ± 1130.6	1945.7 ± 1160.0	
Range	520–4170	436–3530	
Gestational age, wk			.57
Mean ± SD	33.6 ± 5.4	32.5 ± 6.1	
Range	23.7–40.6	23.7–40	
Age at study initiation, d			.05
Mean ± SD	87.6 ± 89.0	40.3 ± 53.9	
Range	1–270	0–142	

Table 2. Parenteral Nutrition (PN) Characteristics and Selenium Dosing.

Variable	Shortage Period (n = 22)	Nonshortage Period (n = 15)	*P* Value
No. of PN days			.02
Mean ± SD	121.0 ± 86	71.5 ± 38.1	
Range	8–301	16–138	
Average PN selenium dose, μg/kg/d			<.0001
Mean ± SD	2 ± 1.2	3.8 ± 1	
Range	0.2–4.6	2.4–6.0	

patient, to take into account correlations among multiple measurements of serum selenium on individual subjects. Findings were considered significant at a *P* value of .05. Data were analyzed using SAS software release 9.3 for Windows (copyright SAS Institute Inc, SAS and all other SAS Institute Inc product of service names are registered trademarks or trademarks of SAS Institute Inc, Cary, NC, USA).

Results

A total of 49 patients met study inclusion criteria. Of these, 12 patients received PN during a period that included time points that overlapped in both the shortage and the nonshortage periods and were thus excluded from the primary analysis. Of the 37 patients included in the primary analysis, 22

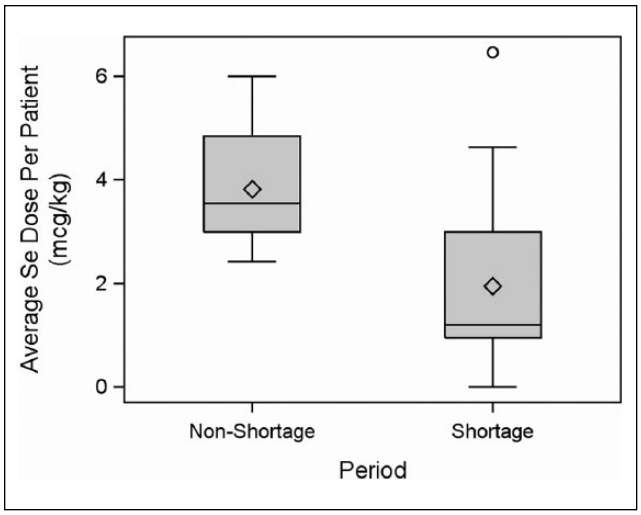

Figure 1. Average selenium (Se) dose per patient. This figure represents the average selenium dose per patient (μg/kg/d) across the shortage and nonshortage periods. The mean dose of selenium provided was significantly higher during the nonshortage period (3.8 ± 1 μg/kg/d) compared with the shortage period (2 ± 1.2 μg/kg/d; $P < .0001$).

received PN during the shortage period and 15 during the nonshortage period. There were no significant differences in baseline characteristics between groups (Table 1), except for age at initiation of the study. Patients in the shortage period were found to be significantly older at the time of the study compared with those in the nonshortage period (87.6 ± 89 days vs 40.3 ± 53.9 days, $P = .05$). The mean number of PN days (Table 2) for the shortage group was 121 ± 86 days and was 71.5 ± 38.1 days for the nonshortage group, $P = .02$. The mean dose of selenium provided was significantly higher during the nonshortage period (3.8 ± 1 μg/kg/d) compared with the shortage period (2 ± 1.2 μg/kg/d; $P < .001$; Table 2; Figure 1).

To address our primary outcome measure of selenium deficiency, biochemical selenium deficiency (Table 3) was expressed in 2 ways: (1) the percentage of serum selenium levels found to be in the deficient range and (2) the total number of patients in each group found to have at least 1 serum selenium level below the lower limit of normal. Of 67 serum selenium levels that were drawn during the shortage period, 45.6% were found to be in the deficient range. Similarly, of 39 levels drawn during the nonshortage period, 46.2% were found to be in the deficient range. These differences were not found to be statistically significant ($P = .96$). Surprisingly, the total number of patients exhibiting biochemical selenium deficiency in the shortage period (n = 13; 59.1%) and the nonshortage period (n = 10; 66.7%) was also found to be similar, $P = .13$.

An estimate of the costs associated with the increase in monitoring secondary to the selenium shortage is displayed in Table 4. Although the difference was not significant, patients in the shortage period had an increased number of serum selenium laboratory draws (3.1 ± 1.8) as compared with those in the nonshortage group (2.6 ± 2.3). This resulted in an average cost increase of $13 per patient for laboratory draws alone. In addition, for patients treated in the outpatient setting with PN provided by the home infusion company affiliated with our institution, the outsourced, compounded product cost $15 per 10 mL, compared with $2.11 per 10-mL vial of the commercial product. Thus, the acquisition cost of the compounded product was approximately 7 times the cost of the commercially manufactured product, leading to an observed cost increase associated with provision of adequate selenium supplementation for patients receiving home PN. Additional costs associated with the selenium shortage, including increased phlebotomy and nursing time, as well as additional pharmacist time managing shortages, were more difficult to quantify but nonetheless should be acknowledged as factors increasing total costs during times of shortage.

No clinically detectable selenium deficiency syndromes were identified during either study period. The impact of the selenium shortage on clinical outcomes proved to be difficult to evaluate because of missing data secondary to the study's retrospective design and the fact that evaluation of clinical markers linked with selenium deficiency are not part of routine care. Many patients did not have all clinical tests completed or laboratory parameters drawn, while others lacked serial data points to use for comparison. Echocardiograms were performed in 18 of the 22 patients in the shortage group and in 10 of the 15 patients in the nonshortage group. While difficult to interpret because of the presence of confounding clinical conditions such as congenital cardiac malformations, an approximately equal number of patients in both groups (55.6% in the shortage group and 50% in the nonshortage group) had some cardiac abnormality noted on echocardiogram, although echocardiogram abnormalities were nonspecific to selenium status. While confounding clinical conditions were also present and the exact impact of concomitant selenium deficiency is unknown, it remains possible that biochemical deficiency had some influence on the observed cardiac abnormalities.

Secondary Analysis

The similar incidence of biochemical selenium deficiency observed during the shortage and the nonshortage period was an unexpected finding; therefore, a secondary analysis was performed to evaluate whether the severity of biochemical deficiency differed between groups. The severity of biochemical deficiency was evaluated in 2 ways: (1) the percentage below the lower limit of age-specific normal serum selenium concentration and (2) the magnitude below the lower limit of age-specific normal serum selenium concentrations. Interestingly, no statistically significant difference was observed between the 2 groups (Table 5). During the shortage period, the average percentage below the lower limit of normal selenium concentration was 28.4% vs 22.1% for shortage and the nonshortage periods, respectively

Table 3. Biochemical Selenium Deficiency.

Variable	Shortage Period (n = 22)	Nonshortage Period (n = 15)	*P* Value
Percentage of levels in deficient range (total no. drawn)	45.6 (67)	46.2 (39)	.96
Total no. of patients with deficiency (%)	13 (59.1)	10 (66.7)	.13[a]

[a]*P* value, controlling for parenteral nutrition exposure time.

Table 4. Secondary Outcomes: Cost.

Variable	Shortage Period (n = 22)	Nonshortage Period (n = 15)	*P* Value
Average selenium laboratory draws per patient	3.1 ± 1.8	2.6 ± 2.3	.47
Average number of laboratory draws per patient per month (95% confidence interval)	0.77 (0.6–0.97)	1.09 (0.80–1.49)	.08
Average per-patient cost associated with serum selenium laboratory draws ($26 per test)	$80.60	$67.60	N/A

Table 5. Magnitude of Biochemical Selenium Deficiency.

Variable	Shortage Period (n = 22)	Nonshortage Period (n = 15)	*P* Value
Average percentage below lower limit of normal	28.4 ± 14.4	22.1 ± 10.0	.25
Average magnitude below the lower limit of normal, ng/mL[a]	15.7 ± 21.2	10.9 ± 14.7	.14

[a]Age-specific reference ranges (ng/mL): 0–2 months: 45–90; 3–6 months: 50–120; 7–9 months: 60–120; 10–12 months: 70–130.

(*P* = .25). The average magnitude below the lower limit of normal of serum selenium measurements was greater during the shortage period: 15.7 ng/mL for the shortage group compared with 10.9 ng/mL for the nonshortage group; however, this difference was not significant, *P* = .14.

A final additional analysis was performed to evaluate the relationship between serum selenium concentration and the intravenous selenium dose provided. All 49 patients meeting study inclusion criteria were included in this analysis. A linear relationship was observed between intravenous selenium dose and serum levels when accounting for the average dose provided over the 7 days prior to the measurement of the serum selenium concentration (Figure 2). Biochemical selenium deficiency was observed more commonly at lower doses. At doses of ≤2 μg/kg/d, nearly 100% of infants were found to be deficient, $P < .01$. When doses of 3 μg/kg/d were provided, an approximately equal chance of deficiency and sufficiency was found (47% deficient vs 53% sufficient), and when doses of ≥6 μg/kg/d were provided, the incidence of selenium deficiency was decreased. Because the number of patients receiving supplementation at >6 μg/kg/d was small, statistical significance could not be calculated for these doses. The linear relationship is represented by the following equation: desired serum selenium concentration = 37.5 + 3.78 × (average dose of selenium provided over the previous 7 days), $r^2 = 0.42$. The same analysis was run using a 14-day lag period, and results were identical. Using this equation, standard doses of at least 6 μg/kg/d would be expected to result in serum selenium concentrations within the normal range most of the time.

Discussion

Nutrition-related product shortages remain an ongoing problem, especially for PN-dependent patients, and the clinical impact of these shortages is not well described in the literature to date. Nutrition support providers are faced with difficult decisions about optimal management during periods of suboptimal product supply, and there is little evidence available to guide practice during shortages. The recommended approach of reducing doses is both logical and necessary to conserve existing supplies[23]; however, the results of this study demonstrate that biochemical selenium deficiency is common and challenges the recommendation to reduce doses during periods of shortage.

This study represents the first evaluation of the impact of the nationwide selenium shortage on PN-dependent infants. Interestingly, no difference was observed in the number of infants found to have biochemical selenium deficiency during the shortage period compared with those treated before the shortage. The magnitude of deficiency was found to be similar between the groups as well. Importantly, roughly two-thirds of infants were observed to be selenium deficient across all time periods. This high rate of biochemical deficiency is a striking finding and indicates that, even when providing a standard dose of 3 μg/kg/d, the development of biochemical selenium

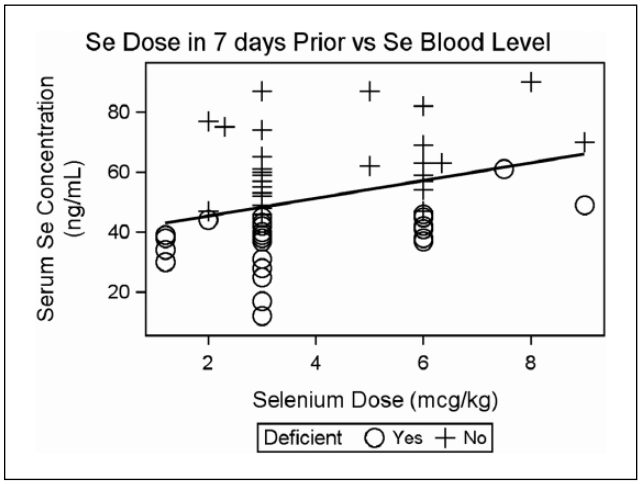

Figure 2. Relationship between selenium (Se) dose and serum selenium levels. This figure represents the relationship between the dose of selenium provided (μg/kg/d) and serum selenium concentrations (ng/mL). A linear relationship is observed expressed by the following equation: Desired serum selenium concentration = 37.5 + 3.78 × (average dose of selenium provided over the previous 7 days), $r^2 = 0.42$. Reference ranges for normal selenium levels are 0–2 months, 45–90 ng/mL; 3–6 months, 50–120 ng/mL; 7–9 months, 60–120 ng/mL; and 10–12 months, 70–130 ng/mL.

deficiency is still a common occurrence. The observed linear relationship between selenium provision and serum selenium concentrations demonstrates that as higher doses of selenium are provided, the incidence of biochemical selenium deficiency decreases. Although the r^2 value calculated was not extremely high, we believe that it shows a strong enough relationship between intravenous selenium dose and serum selenium to be of value in assessing how changes in intravenous selenium dose may relate to serum selenium concentrations. While further studies are warranted to determine the optimal dose of intravenous selenium to prevent biochemical deficiency and deficiency syndromes, as well as to validate the linear relationship, these results suggest that empiric doses of 4–6 μg/kg/d may be needed to prevent deficiency and that even higher doses of up to 9 μg/kg/d may be necessary to treat patients who develop biochemical deficiency. Determination of optimal management of scarce resources is a challenge for clinicians. However, our results suggest that rather than conserving supplies by providing decreased doses to all patients, thus putting larger groups of patients at risk for developing deficiency, an alternative approach to consider is targeted treatment of the most vulnerable populations with individualized doses needed to prevent and/or treat deficiency, as supplies allow.

There are several limitations to this investigation. First, this study was retrospective in nature, which resulted in missing data and the inability to evaluate clinical manifestations of deficiency. For this evaluation, serum selenium levels were used as the biomarker of selenium status and considered diagnostic of selenium deficiency; however, it is important to note that serum levels may decrease during trauma, critical illness, and with systematic inflammatory conditions.[5,11,22] Thus, interpretation should ideally be done in conjunction with markers of inflammation, such as C-reactive protein. In addition, serum selenium levels may be below normal for prolonged periods of time prior to development and manifestation of clinical symptoms.[24,28,30] The length of time between observation of low serum selenium levels and manifestation of clinical symptoms is not well elucidated. Overt symptoms of selenium deficiency are often nonspecific and may be due to multiple other factors; an example of this is concurrent iodine deficiency in hypothyroidism.[9,30] Despite these complications and limitations in interpretation, in clinical practice, serum selenium concentrations remain the most practical measure available for assessment of selenium status, and it is felt prudent to use this as an early marker of selenium status. This approach allows the clinician to make the necessary dose adjustments earlier in treatment so that the serious long-term complications of selenium deficiency, such as cardiomyopathy, can be prevented.

Another limitation to this study is that there may have been heterogeneity in the manner in which infants were monitored during the 2 study periods. Specifically, during the nonshortage period, long-term PN patients had serum selenium concentrations routinely monitored on a monthly basis. During the shortage periods, patients may have been monitored more frequently because of the possibility of increased risk for development of biochemical deficiency, which may have led to identification of deficiency earlier in the course of therapy. However, the similar incidences of biochemical selenium deficiency observed indicate that the potential differences in monitoring had little effect on the primary outcome. Furthermore, evaluation of baseline serum selenium concentrations is not currently a standard practice at our institution; therefore, the observed deficiencies cannot be conclusively linked to the doses provided, and the possibility exists that infants were born with a biochemical selenium deficiency. Similarly, the time course to development of biochemical selenium deficiency was unable to be accurately determined. As serum selenium levels were typically obtained every 2–4 weeks, it is possible that deficiencies occurred prior to serum concentration measurements. Therefore, although we did not observe a difference in the overall number of patients who developed deficiencies between the groups, it is possible that patients receiving reduced doses developed deficiency earlier in therapy than those receiving standard and individualized doses.

This study excluded patients who exclusively received oral selenium supplementation. During periods of shortage, provision of oral supplementation, with concurrent removal of intravenous selenium from PN, has become routine practice for patients receiving ≥50% of calories from enteral nutrition. The impact of the intravenous selenium product shortage on the frequency of this practice was not evaluated in this study. Similarly, this study did not account for concomitant enteral feeds, a potential additional source of selenium supplementation; this decision was guided by the variations in enteral

absorption observed in PN-dependent infants with intestinal failure. Although this may have affected the study results, the high number of infants observed to be selenium deficient indicates that even if enteral absorption of selenium occurred, it had little impact on the overall development of biochemical deficiency.

Finally, the cost impact of the shortage was only qualitatively described and was limited to the cost of obtaining serum selenium levels and product acquisition costs. Other expenses, such as nursing and phlebotomy time for laboratory draws, as well as time spent managing product shortages (eg, time spent researching and acquiring alternative products, adjusting PN orders, etc), were not quantified. During the shortage period, infants receiving PN at home had access to an outsourced, compounded intravenous selenium product through a reputable compounding pharmacy. However, since the time of this study, new regulations were enacted, strengthening U.S. FDA oversight of compounding pharmacies.[31] The Drug Quality and Security Act, enacted on November 27, 2013, added a new section to the Federal Food, Drug, and Cosmetics Act (section 503b), which established regulated entities known as outsourcing facilities.[31,32] As a consequence of the new legislation, outsourced selenium products will no longer be available to patients receiving home PN from our institution.

Despite the limitations listed above, this study provides important insight into the impact of the selenium shortage and provides much-needed data that may be used to guide practice in this era of ongoing nutrition-related product shortages. The high incidence of biochemical selenium deficiency, regardless of product shortage status, is critical to consider when making management changes when supplies are scarce. Roughly two-thirds of all infants evaluated were found to have biochemical selenium deficiency, even when recommended doses were provided; this result suggests that those dependent on long-term PN may need a higher baseline dose and that further prospective investigation is necessary to determine the appropriate empiric dosing of intravenous selenium. Such investigations may result in revision of PN guideline recommendations; however, these studies will be possible only if intravenous selenium products are reliably available. As of September 2014, intravenous selenium remains on shortage with no estimated date to complete restoration of supply.[26,27] While overt clinical signs and symptoms may take years to develop, the current shortage began in 2011, and adverse clinical outcomes may soon emerge in the most vulnerable patient populations. Until consistent and sufficient product supplies are available, clinicians will continue to be faced with challenges in managing and meeting the nutritional needs of PN-dependent patient populations.

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Statement of Authorship

All authors contributed to the conception/design of the research, contributed to the acquisition, analysis, or interpretation of data, and drafted and critically revised the manuscript. All authors gave final approval of the manuscript and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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