Selenium supplementation in pediatric patients using parenteral nutrition: Is it time to do something?

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Summary

Objective: To analyze the nutritional status of selenium and verify the effect of its supplementation in pediatric patients during 14 days of parenteral nutrition (PN).

Method: This is a series of cases with patients followed for two weeks while using PN. Data collection was performed at the beginning (T0), in the 7th (T1) and 14th days of PN (T2). The supplemented group received 2 µg/kg/day of selenous acid. Weight and height were measured for nutritional status assessment. Tests requested: plasma selenium, albumin, pre-albumin, C-reactive protein (CRP), total cholesterol and HDL-cholesterol.

Results: Fourteen (14) patients with inflammatory process and with low or very low weight for their ages were evaluated. In both groups (with and without supplementation), all patients had low selenium levels. Median plasma selenium concentrations were 17.4 µg/L (T0), 23.0 µg/L (T1) and 20.7 µg/L (T2). Increase and reduction of selenium occurred both in patients with high CRP and in those presenting normalization of this parameter.

Conclusion: Lower plasma selenium levels have been detected since the start of the research and supplementation (2 µg/kg/day of selenous acid) was not to enough to approach the reference values.

Keywords: Selenium. C-reactive Protein. Supplementary Feeding. Parenteral Nutrition. Child.

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Introduction

The essentiality of selenium to human health and the benefit this mineral adds to nutritional therapy from the first days following birth has been reported in recent decades.[1,2] In fact, selenium deficiency is associated with cardiomyopathy, prematurity, and clinical and nutritional changes.[1-4]

Considering that patients with inflammation have an exacerbated oxidative process and that selenium is an important component of glutathione peroxidase (GPx), an antioxidant enzyme, it has been assumed that these patients must present an increased need for selenium.[1,4]

Some studies have revealed selenium deficiency in patients using parenteral nutrition (PN), who had not been supplemented with selenium for an extended period of time.[3,4] As such, it has been stated that supplementation should be indicated when PN is used for a period lasting longer than four weeks[3] or after two weeks of PN when this is the main source of nutrition.[5] Since 2012, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends the addition of 2 µg/kg/day of selenium in all pediatric PN formulas from the start of PN.[6,7]

Selenium supplementation seems to contribute to a reduction in mechanical ventilation time, improved weight gain, decreased risk of sepsis and the prevention of cardiomyopathy.[1,2,4,8] However, this is not a commonly used practice, unlike other trace elements such as zinc, copper, chromium and manganese.

In several countries, including Brazil, PN formulas and trace element solutions do not contain selenium. The current alternative to supplementation is to add it separately. However, the beginning of supplementation, supplementation time, the selenium compound offered and the amount of selenium that should be offered are still under discussion in the literature.[1,4] Thus, the objective of our study was to analyze the nutritional status related to selenium and

to verify the effect of supplementation with this mineral in pediatric patients during 14 days of PN.

Method

Study characteristics

This is a prospective study of a case series of patients monitored during two weeks of use of PN. The inclusion criteria were: pediatric patients (aged 0 to 18 years); use of PN as the main source of nutrition (> 80% of nutritional needs); hospitalization at the Hospital de Clínicas da Unicamp; absence of kidney failure due to the risk of intoxication and signing of an Informed Consent Form by the person responsible for the patient.

Data collection was performed at the beginning (T0) and on the 7th (T1) and 14th day of PN (T2). This study was approved by the Ethics and Research Committee of the Unicamp Medical School (No. 538/2011).

Indication and prescription of PN

Parenteral nutrition was monitored by the Multiprofessional Nutritional Therapy Team (EMTN), composed by a nutritionist, nurse, pharmacist and two pediatric physicians that were specialists in PN and enteral nutrition (EN). The prescription of individualized PN was performed by the EMTN physician in accordance with the recommendations of ASPEN[9] and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).[10] When there were laboratory abnormalities, such as mineral disturbances, it was necessary to re-individualize them in accordance with the permitted pharmacotechnical limits. The pharmacochemical guidelines were followed and attested by the EMTN pharmacist, and the compounding company that makes the solutions, according to the MS/SUS Ordinance No. 272 of April 8, 1998.[11] After randomization, the supplemented group received 2 µg/kg/day of selenous acid via PN, according to the ASPEN recommendation.[6]

Nutritional status assessment

Anthropometry was performed based on weight and height measurements according to the World Health Organization (WHO)[12] and Lohman et al.[13] The equipment used in the measurement were a stadiometer (with 0.1 cm precision) and Filizola® electronic digital scales (capacity from 2.5 kg to 150 kg), as well as Toledo® electronic scales (capacity from 0.1 kg to 15 kg). With the data collected in the anthropometric assessment, the nutritional status was classified in accordance with that proposed by the WHO:[12,14]

- Weight/age: very low weight for age (z score < -3); low weight for age (z score between -3 and -2); suitable weight for age (z score ≥ -2 and ≤ +2); high weight for age (z score > +2).
- BMI/age (patients over 10 years of age): accentuated thinness (z score < -3); thinness (z score between -3 and -2); eutrophy (z score ≥ -2 and ≤ +1); overweight (z score between +1 and +2); obesity (z score between +2 and +3); severe obesity (z score > +3). BMI/age was not used in patients less than 10 years of age due to the difficulty in measuring height, especially in patients admitted to the intensive care unit (ICU).

Selenium status evaluation

For the determination of plasma selenium levels, 1 mL of blood was collected in dry tubes (free of trace elements) then centrifuged for plasma separation and stored at -20°C. The plasma samples were digested (via an acid) in Pyrex glass tubes containing 5 mL of nitric acid 68% P.A (Merk) and allowed to rest overnight. Subsequently, a digester block with an initial temperature of 50°C was used for the digestion, gradually increasing to 150°C (the maximum) for elimination of organic substances and reduction of selenium to IV selenium. Subsequently, 5 mL of 1.2 N HCL were added to the samples which were heated at 100°C for two hours. The solutions were then diluted to 25 mL with deionized water and submitted to selenium reading.[14-18] The method used in the reading was hydride generation atomic absorption spectrometry coupled to the quartz cell (HGQTAAS) (model Z5000, Hitachi, Tokyo, Japan) at the Laboratory of Nutrition – Minerals at the Pharmaceutical Sciences School of the University of São Paulo (USP). All materials used during the analysis and dosage of selenium were demineralized with a 30% nitric acid bath for at least 12 hours and rinsed 10 times consecutively with deionized water. As there are no reference values for the Brazilian pediatric population, we considered values ≥ 40 µg/L as normal. These values are within the normal range described in several studies with the same population.[4,7,19-21]

Laboratory assessment of the clinical picture

The other laboratory tests used in the research were those routinely used to accompany the patient in PN. Dosage and blood collection were performed by the Clinical Pathology Laboratory team of the Hospital de Clínicas. The exams computed, the method used and the values of normality are shown in Table 1.

Statistical analysis

The statistical treatment of the collected data was performed with the help of the Statistical Package for the Social Sci-

TABLE 1 Dosage method and values of normality used by the Laboratory of Clinical Pathology of the Hospital de Clínicas da Unicamp.

Laboratory tests	Investigation method	Reference values
Pre-albumin	Nephelometry	20-40 mg/dL
Albumin	Colorimetric (bromocresol green)	≤ 4 days: 2.8-4.4 g/dL
		≥ 5 days: 3.5-5.2 g/dL
C-reactive protein	Nephelometry	< 0.3 mg/dL
Total cholesterol	Enzymatic – colorimetric	2-19 years < 170 mg/dL
HDL-cholesterol	Enzymatic – direct colorimetric	< 10 years: desirable: ≥ 40 mg/dL
		10-19 years: desirable ≥ 35 mg/dL

ences® software version 17 (SPSS). An exploratory analysis was performed using summary measures (median, mean, standard deviation, minimum, maximum and frequency).

Results

The sample consisted of 14 pediatric patients undergoing PN that were hospitalized, mainly in the pediatric ICU, with an ongoing inflammatory process (evidenced by high C-reactive protein – CRP) and low or very low weight for age (Table 2).

Low plasma selenium concentrations were observed in all patients throughout the study, including patients who showed improvement in CRP and pre-albumin levels on day 14 (Table 3).

Table 4 shows that no patient had selenium levels within the reference range (n = 7/7) and CRP was high in only three cases after 14 days of evaluation.

Supplemented group

Among the four supplemented patients (numbers 11, 12, 13 and 14), all were male, two were hospitalized in the pediatric ICU and one died. Patient number 11, who died, started PN with selenium plasma levels below the reference range and which progressively decreased throughout the three assessment times. Albumin was low, and pre-albumin, which was initially normal, decreased. CRP fell in the third assessment but was still above the reference values. This patient was diagnosed with primary immunodeficiency and inflammatory disease.

Among the other three supplemented patients (numbers 12, 13 and 14), none reached normal levels. Patient number 14, who reached the closest levels (34.9 µg/L) of the reference, had normal albumin and pre-albumin, which started low and became normalized after the second dose. CRP concentrations started high but decreased and reached the reference range. Furthermore, the patient had an adequate weight.

Non-supplemented group

Among the ten non-supplemented patients, it was not possible to perform the second and third blood levels measurements in three cases (numbers 1, 3 and 6). Among these, all had low selenium concentrations and, above all, the values were lower for those who died (number 1 and 3). Meanwhile, patient number 6, who was discharged, had plasma selenium of 34.4 µg/L (close to normal) and CRP of 2.25 mg/dL.

Regarding the other seven non-supplemented patients, death occurred in three cases (numbers 5, 7 and 10). Among these, it was verified that patient number 10, with the most critical selenium levels (6.3 µg/L), had adequate CRP (0.18 mg/dL).

In general, after 14 days of assessment, selenium levels did not reach the reference values (patients 2, 4, 8, 9 and 10) and CRP was high in two cases (numbers 4 and 9).

Discussion

The sample consisted mainly of patients hospitalized in the pediatric ICU with an ongoing inflammatory process (evidenced by high CRP and low high density lipoprotein [HDL], pre-albumin and albumin values) and low or very low weight for age. All of the patients evaluated had plasma selenium levels below the reference values throughout the study. Among those patients receiving supplementation (2 µg/kg/day of selenium as selenous acid), it was found that this was insufficient for the normalization of plasma levels over 14 days.

In clinical practice, plasma selenium appears to be the best marker of the nutritional status of individuals in relation to selenium.[7] Unlike erythrocyte selenium, plasma selenium reflects the current nutritional status in relation to the mineral[22] and is the most commonly used marker in general.[7] However, for adequate interpretation of the plasma parameters related to selenium, the dosage of CRP and HDL-cholesterol is required. After all, elevation of CRP (acute phase protein) and reduction of HDL is what characterizes

TABLE 2 Description of patients according to age, place of hospitalization, outcome, nutritional status, main diagnosis and PN indication.

Patient	Age	Hospitalization setting	Outcome	Z score	Nutritional status classification	Days before PN[d]	Main diagnosis	PN indication
1	5 months	PICU	Death	-6.39[b]	Very low weight	112	CHF + kidney failure + sepsis	Subocclusion (clinical)
2	5 years	PICU	Non-death	-1.43[b]	Normal weight	65	Volvulus	SBS (surgical)
3	8 months	PICU	Death	-5.28[b]	Very low weight	99	Cerebral palsy	Refractory diarrhea + SBS (clinical)
4	13 years	WARD, PED	Non-death	–	–	7	Myelomeningocele	Fistula (surgical)
5	2 days	PICU	Death	-0.99[b]	Normal weight	0	Congenital heart disease	Ileum (surgical)
6	7 months	PICU	Non-death	-2.12[b]	Low weight	4	Bowel cancer	Ileum (surgical)
7	4 months	PICU	Death	-3.78[b]	Very low weight	7	Septic shock	Ileum (clinical)
8	15 years	WARD, PED	Non-death	-3.12[c]	Severe emaciation	1	Pancreatitis	Pancreatitis (clinical)
9	1 year	PICU	Non-death	-7.04[b]	Very low weight	78	Rubinstein-Taybi syndrome	Chylothorax (clinical)
10	5 years	WARD, PED	Death	-0.74[b]	Normal weight	28	CMPA + colectomy + SBS	SBS (surgical)
11[a]	3 years	PICU	Death	-1.41[b]	Normal weight	10	Primary immunosuppression + Crohn's disease	LGIB (clinical)
12[a]	11 years	PICU	Non-death	-3.13[c]	Severe emaciation	4	GI paresis + GI distension + meningitis	Ileum (clinical)
13[a]	1 year	WARD, PED	Non-death	-3.6[b]	Low weight	6	Gastroschisis + CMPA	Ileum (surgical)
14[a]	4 months	WARD, PED	Non-death	-1.43[b]	Normal weight	2	Congenital diaphragmatic hernia + Crohn's disease	Ileum (clinical)

PICU: pediatric intensive care unit; WARD, PED: pediatric ward; PN: parenteral nutrition; CHF: congestive heart failure; CMPA: cow's-milk protein allergy; SBS: short bowel syndrome; LGIB: lower gastrointestinal bleeding; GI: gastrointestinal.
[a]Supplemented with selenous acid (2 µg/kg/day); [b]weight/age; [c]BMI/age; [d]days of hospital stay before the beginning of PN.

TABLE 3 Evolution of the biochemical tests in the three points of evaluation.

Tests	N	Mean (SD)	Median	Range	Altered results
Selenium (µg/L)					
Time 0	14	20.83 (8.71)	20.67	6.50-34.46	14/14 (↓)
Time 1	10	17.39 (5.16)	17.43	6.50-24.46	10/10 (↓)
Time 2	9	20.6 (9.60)	23.05	6.22-34.93	9/9 (↓)
CRP (mg/dL)					
Time 0	11	9.84 (11.33)	4.78	0.04-33.10	10/11 (↑)
Time 1	7	4.70 (6.10)	3.24	0.02-17.00	5/7 (↑)
Time 2	6	2.07 (2.14)	1.83	0.02-4.42	3/6 (↑)
Pre-albumin (mg/dL)					
Time 0	14	14.16 (8.69)	11.40	5.46-38.50	11/14 (↓)
Time 1	10	22.09 (12.06)	20.70	9.47-41.60	5/10 (↓)
Time 2	7	25.91 (14.04)	20.70	11.40-45.60	3/7 (↓)
Total cholesterol (mg/dL)					
Time 0	12	1.08 (41.87)	96.00	50.00-193.00	2/12 (↑)
Time 1	10	1.27 (54.18)	1.195	48.00-201.00	2/10 (↑)
Time 2	6	1.60 (59.82)	1.40	101.00-261.00	2/6 (↑)
HDL-cholesterol (mg/dL)					
Time 0	12	23.42 (8.51)	23.00	10.00-42.00	11/12 (↓)
Time 1	10	22.30 (12.93)	22.50	7.00-44.00	8/10 (↓)
Time 2	7	35.86 (13.03)	36.00	16.00-58.00	4/7 (↓)
Albumin[a] (g/dL)					
Time 0	12	3.46 (0.82)	3.65	1.90-4.70	7/14 (↓)

SD: standard deviation; CRP: C-reative protein; (↑) above the reference value; (↓) below the reference value; [a]albumin was dosed only once because of long half-life (21 days).

TABLE 4 Evolution of plasma selenium and C-reactive protein concentration of each patient over the three evaluation points.

Patient	Selenium T0 (µg/L)	CRP T0 (mg/dL)	Selenium T1 (µg/L)	CRP T1 (mg/dL)	Selenium T2 (µg/L)	CRP T2 (mg/dL)	Behavior of selenium[c]
1[a]	17.7	1.54	–	–	–	–	–
2[a]	13.4		10.9	0.02	23.0	0.02	9.6 (↑)
3[a]	20.9	17.4	–	–	–	–	–
4[a]	14.6	–	–	–	18.8	4.12	4.2 (↑)
5[a]	6.5	4.78	22.7	–	–	–	16.2 (↑)
6[a]	34.4	2.25	–	–	–	–	–
7[a]	30.9	–	24.4	4.9	–	–	–6.5 (↓)
8[a]	30.8	0.04	14.2	0.02	23.5	–	–7.3 (↓)
9[a]	12.6	26.5	17.0	3.24	24.9	4.42	12.3 (↑)
10[a]	10.6	1.66	17.9	0.37	6.3	0.18	–4.3 (↓)
11[b]	27.8	7.09	19.2	7.39	6.2	3.45	–21.6 (↓)
12[b]	21.9	12.8	23.8	17	29.6	–	7.7 (↑)
13[b]	20.4	1.09	10.6	–	18.7	–	–1.7 (↓)
14[b]	29.0	33.1	13.1	–	34.9	0.22	5.6 (↑)

CRP: C–reactive protein; [a]patient without selenium supplementation; [b]patient supplemented with selenous acid (2 µg/kg/day); [c]evolution from the first to the last investigation; (↑) increase in the levels of selenium; (↓) decline in the levels of selenium.

the inflammatory process,[23-25] and this may contribute to the reduction of plasma selenium values.

In the present study, plasma selenium concentrations were low from the onset of PN and did not reach normal levels over the 14-day follow-up regardless of the CRP and/or supplementation values. This may have occurred due to the supplementation time and/or selenium dosage offered.

In the supplemented group, one patient attained selenium concentrations closer to normal levels after supplementation. In this patient, it is possible that the increase occurred due to the reduction of inflammation (evidenced by the fall in CRP). However, it is also plausible that selenium and CRP values also improved due to the effect of supplementation, since selenium has antioxidant and anti-inflammatory functions.[26]

In an investigation by Leite et al.[21] including infants and children with systemic inflammatory response syndrome, 90.9% of the patients were found to have selenium concentrations below the reference (the mean selenium plasma concentration was 23.4 µg/L). However, even during the acute phase of the inflammatory process, reduced ventilation and ICU length of stay were associated with increased selenium levels, indicating that supplementation may be beneficial in this population.

There is variation between the studies in relation to the supplementation time. In a study by Masumoto et al.,[4] the four surgical patients (use of nutritional support without selenium) who developed a deficiency showed clinical and laboratory improvement after supplementation for more than two months. In a study by Etani et al.[20] with 95 patients aged from 7 months to 20 years with intestinal dysfunction and/or neurological disorders (use of PN and/or EN with little or no selenium), it was found that 28/95 patients presented selenium concentrations below 40 µg/L and clinical manifestations associated with low selenium levels. Among the 28 patients, five presented concentrations below 20 µg/L of selenium, as in our study. After a year of supplementation, the five patients showed improvement in the clinical manifestations.

Regarding the amount of selenium that should be offered, studies suggest selenium supplementation of over 2 µg/kg/day.[4,7] According to the Australasian Society for Parenteral and Enteral Nutrition, selenium requirements in PN can increase, even in the short term (< 20 days) because the current illness or surgical procedure intensifies the metabolic and antioxidant needs.[27,28] For adult patients, the ASPEN[6] recommends 60-100 µg/day of selenium and mentions that, in cases of inflammatory process, the supply should be close to the upper or surplus limit without exceeding 400 µg/day. However, this observation regarding the inflammatory process was not made for the pediatric population.

In addition to the inflammatory process and metabolic stress, age can also be a risk factor for selenium deficiency. The most susceptible to deficiency are infants, as they store less selenium and therefore have a lower stock than children and adults.[29]

In relation to nutritional status, the assessment with laboratory tests was complex given that albumin and pre-albumin undergo changes due to the inflammatory process.[30] However, according to the anthropometric assessment, the majority of patients were evaluated as having severe malnutrition, another factor that can influence the body's demand and nutrient reserves, and harm a patient's prognosis.

In fact, the selenium values detected in our study were similar to or lower than those observed in other studies, which associated low levels of selenium with diseases and serious clinical complications.[4,18-21] Therefore, laboratory monitoring of plasma selenium may contribute to the prevention of a number of future complications with the use of supplementation from the start of PN in patients undergoing the inflammatory process.

Limitations of the study

The number of patients reported was lower than desired due to death or withdrawal from PN before the 14th day of monitoring. Furthermore, the diversity of diseases, clinical complications and age range of the patients characterized a heterogeneous and complex sample. However, heterogeneity is a feature commonly found in intensive care – which was the hospitalization setting of most of the patients studied. The indication of selenium supplementation for pediatric patients does not vary according to the underlying disease, age and intensity of inflammation.

Conclusion

Plasma selenium levels were very low and supplementation with 2 µg/kg/day of selenous acid was not sufficient for the normalization of these levels. We therefore emphasize the importance of monitoring selenium status and supplementation from the onset of PN in patients undergoing the inflammatory process. However, it should be noted that more studies are needed in order to establish the amount of selenium supplied and the appropriate time of intervention.

Resumo

Suplementação de selênio nos pacientes pediátricos em uso de nutrição parenteral: é hora de fazer algo?

Objetivo: Analisar o estado nutricional relativo ao selênio e verificar o efeito da suplementação desse mineral em pacientes pediátricos durante 14 dias de nutrição parenteral (NP).

Método: Trata-se de estudo prospectivo de uma série de casos de pacientes acompanhados durante duas semanas de uso de NP. A coleta de dados foi realizada no início (T0), no 7º (T1) e no 14º dia de NP (T2). Após randomização, o grupo suplementado recebeu 2 µg/kg/dia de ácido selenioso. Peso e altura foram aferidos para avaliação do estado nutricional. Exames coletados: selênio plasmático, albumina, pré-albumina, proteína C-reativa (PCR), colesterol total e HDL-colesterol.

Resultados: Foram avaliados 14 pacientes com processo inflamatório em curso e com baixo ou muito baixo peso para a idade. Os pacientes (grupo suplementado e não suplementado) tinham baixas concentrações de selênio. A mediana dos valores de selênio plasmático foi de 17,4 µg/L (T0), 23,0 µg/L (T1) e 20,7 µg/L (T2). Aumento e redução de selênio ocorreram tanto nos pacientes com PCR elevada quanto naqueles que apresentaram normalização desse parâmetro.

Conclusão: Os níveis de selênio detectados foram muito baixos e a suplementação (2 µg/kg/dia de ácido selenioso) não foi suficiente para normalização dos níveis plasmáticos.

Palavras-chave: Selênio. Proteína C-reativa. Suplementação Alimentar. Nutrição Parenteral. Criança.

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