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Vitamin Serum Level Variations Between Cycles of Intermittent Parenteral Nutrition in Adult Patients With Short Bowel Syndrome

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Abstract

Background: An alternative form of nutrition therapy for patients with short bowel syndrome (SBS) who do not have home parenteral nutrition (PN) available is the administration of the PN cycle during regular hospital admissions and oral vitamin supplement at home. The aim of this study was to evaluate serum levels of folic acid and vitamins A, B_{12}, C, and E before and after the PN cycle in patients with SBS. *Materials and Methods:* This research was conducted with 10 patients with SBS (less than 15 minutes of total barium transit time) who were receiving the PN cycle and oral vitamin supplement at home. Patients were evaluated regarding total food ingestion and oral vitamin supplement intake. Serum levels of vitamins were evaluated immediately after the end of each PN cycle (phase 1) and before the beginning of the next PN cycle (phase 2). *Results:* Patients' nutrient ingestion was in accordance with recommendations for healthy individuals. Regarding the oral vitamin supplement intake, 20% of the patients presented low adherence. Although all patients had a normal serum level of folic acid and vitamin B_{12}, PN vitamin infusion during hospitalization and home oral vitamin supplement were not enough to make the serum levels of vitamins A, C, and E achieve normal values. *Conclusion:* This study documented that patients did not receive an adequate administration of oral vitamin supplements of vitamins A, C, and E through PN. More studies need to be conducted investigating higher doses of vitamin administration (oral or intravenous administration), assessing differences between water and liposoluble supplements. (*JPEN J Parenter Enteral Nutr*. 2013;37: 75-80)

Keywords

short bowel syndrome; serum vitamins; parenteral nutrition; nutrition assessment; clinical pharmacy

Clinical Relevancy Statement

In Brazil, as home parenteral nutrition (PN) is not a therapeutic option provided by the Brazilian Public Health System, a form of nutrition therapy available for patients with severe malabsorption is the administration of PN in cycles, during regular hospital admissions, adjusted according to individual needs. Considering the differences between the PN cycle and home PN, the clinical outcomes may be slightly different due to the time between the administration period and the regularity in administration. The present group of researchers is not aware of other studies that have evaluated vitamin status throughout PN cycle intervals in patients with severe impairment of absorptive capacity.

Introduction

Short bowel syndrome (SBS) occurs when a patient undergoes an intestine resection and <200 centimeters of functional small intestine is maintained. Patients with SBS have to deal with numerous healthcare provider recommendations, such as changes in behavior and lifestyle, changes in dietary habits, and the use of drugs to minimize diarrhea and clinical manifestations of nutrition deficiencies.[1,2] In the most severe cases, patients are not able to achieve their nutrition needs and become dependent on parenteral nutrition (PN)[3] to avoid nutrition deficiencies, such as xerophthalmia,[4,5] muscle weakness,[6] and neurological manifestations.[7]

In many countries, patients with SBS receive PN at home, which improves long-term survival and quality of life, without exposition to a prolonged hospital stay.[8]

An alternative to home PN is the administration of PN in cycles at the hospital.[9] While patients who receive the PN cycle are at home, they are encouraged to be adherent to treatment, eating a balanced diet and taking tablets containing minerals and vitamins daily. During this period,

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Table 1. Clinical characteristics of PN-Dependent Patients With SBS.

Patients	Gender	Age, y	BMI, kg/m^2	Time on PN, mo	Small Bowel Length, cm	Cause of SBS	Residual Colon
1	M	63	16.3	95	10	Mesenteric ischemia	From transverse
2	M	44	13.6	36	100	Mesenteric ischemia	From ileocecal valve
3	M	69	23.4	18	25	Mesenteric ischemia	From transverse
4	F	36	16.1	25	15	Mesenteric ischemia	From transverse
5	F	50	18.4	101	20	Mesenteric ischemia	From transverse
6	F	63	18.8	14	30	Mesenteric ischemia	From transverse
7	M	47	15.7	6	60	Crohn's disease resection	None
8	F	48	14.4	12	25	Mesenteric ischemia	From transverse
9	M	71	17.6	4	30	Mesenteric ischemia	From transverse
10	M	71	20.3	3	30	Mesenteric ischemia	From transverse
	6M:4F	56.2 ± 12.7	17.5 ± 2.9	16 (3–101)	27.5 (10–180)		

BMI, body mass index; F, female; M, male; PN, parenteral nutrition; SBS, short bowel syndrome.

the oral route is the only possibility for nutrient and drug administration. For this reason, the design of this study made it possible to assess serum level while patients remained at home, providing information on variations between PN cycles.

The hypothesis of this study was that adequate vitamin supplementation through the digestive route, by means of food and vitamin supplements, would maintain vitamin serum levels in patients with SBS between cycles of PN. Therefore, the aim of this research was to evaluate the variation in the vitamin serum levels between the cycles of PN in PN-dependent patients with SBS.

Casuistic and Methods

This research was conducted at a public referral teaching hospital, after being approved by the institution's ethics committee (#11442/2007). All patients with SBS who were receiving PN as a specialized service at the present institution and who agreed to participate and give written informed consent were eligible for this study. The exclusion criteria were clinically and hemodynamically unstable patients and individuals with active intestinal inflammatory diseases, neoplasia, hepatic failure, and diagnosis of active infectious diseases. The final casuistic included 10 patients with SBS (Table 1), which represented the entire population of patients who were assisted during the research period (August 2008 to November 2009). No patient refused to participate in the study.

All patients with SBS were admitted to the hospital to receive cycles of PN and were evaluated at 2 different times: immediately after the end of each PN cycle (phase 1) and before the beginning of next the PN cycle (phase 2).

At each new admission, patients underwent an extensive examination to ensure that they were clinically and hemodynamically stable and without infection. Beyond those investigations, patients were monitored for fever symptoms and leukogram changes. The site of the catheter's insertion was also investigated regarding the presence of phlogistic signs and, if necessary, were realized culture of blood cells collected from a peripheral vein or at the site of the catheter's insertion. For the collection of the second samples (phase 2), if the patient was clinically and hemodynamically unstable or had any kind of infection, the first sample collected was disregarded and a new sample collection was begun in the following admissions, whenever possible.

During each admission cycle, the patients received PN for 4 ± 2 days, with an interval of 16 ± 6 days between hospitalizations, depending on diarrhea, dehydration, and nutrition status. PN was infused through a totally inserted central venous catheter. The PN solution contained a crystalline amino acid solution (Soramin; Darrow, Rio de Janeiro, Brazil), dextrose (Hiplex; Fresenius Kabi, Campinas, Brazil), lipid emulsion (Lipofundin MCT/LCT; BBraun, Melsungen, Germany), vitamins (Cerne; Baxter, Deerfield, IL), trace elements (Ad-element; Darrow), and electrolytes, according to current recommendations.[10] The composition of the vitamin solution is presented in Table 2.

Centrum (Wyeth, Itapevi-SP, Brazil) was the vitamin and mineral supplement prescribed to be used at home for patients with SBS who were assisted at the present institution. However, there was an alternative prescription, distributed without any cost by the Brazilian Public Health System, for patients who were facing financial difficulties in buying Centrum (Table 3).

Analysis of the composition of the habitual diet was based on the Semi-Quantitative Food Frequency Questionnaire, which assesses food intake for the previous 6 months. The dietetic data were processed by specific software (NutWin 1.5 Professional Software; Federal University of São Paulo, São Paulo, Brazil). Adherence to home oral vitamin supplement intake was assessed by the Morisky test. Adherence was classified into high (answering yes to 0 items), medium (answering yes to 1–2 items), or low (answering yes to 3–4 items) categories.[11] The total supplied amount of oral A, C, and E vitamins was calculated by adding the quantity obtained from the diet plus the amount from the vitamin supplement to verify the

Table 2. Composition of Vitamins Used in the Parenteral Nutrition Solution.

Micronutrient	Concentration per Ampoule
Ascorbic acid	100 mg
Folic acid	400 mcg
Biotin	60 mcg
Cyanocobalamin	5 mcg
Pantothenic acid	15 mg
Riboflavin	3.6 mg
Nicotinamide	40 mg
Pyridoxine	4 mg
Thiamine	3 mg
Retinol	3300 IU
Tocopherol	10 IU
Cholecalciferol	200 IU

possible association with their serum levels. Patients were also questioned about their socioeconomic status.

The patients also underwent routine laboratory evaluation, such as blood glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, hemoglobin, lymphocytes, total proteins, serum albumin, transferrin, C-reactive protein (CRP), and ferritin.

Folic acid and cyanocobalamin were determined by chemiluminescent enzyme immunoassay (IMMULITE kit; Siemens Health Care Diagnostics, Llanberris-GWN, United Kingdom). Ascorbic acid was measured by colorimetric reaction with 2,4-dinitrophenylhydrazine and spectrophotometric detection.[12] Determination of retinol and α-tocopherol was accomplished by ultraviolet high-performance liquid chromatography.[13]

Numeric variables with normal distribution are presented as mean ± standard deviation (SD), and those with nonnormal distribution are presented as median and range. Comparison of quantitative variables between the obtained values at 2 different moments (phase 1 vs phase 2) was made by the Student *t* test for dependent samples or the Wilcoxon paired test, depending on normality and homogeneity of the samples. The Spearman correlation coefficient was calculated to evaluate the degree of correlation between vitamin serum level and variables such as age, body mass index (BMI), time of intestinal resection, and remaining intestine length. Statistical significance was set at $P < .05$. Data analyses were performed with Statistica software (version 8.0; StatSoft, Inc, Tulsa, OK).

Results

The average daily intake was the following: energy, 2138 ± 635 kcal; protein, 82 ± 21 g; carbohydrate, 318 ± 112 g; and lipids, 60 ± 27 g/d. After adjustment for current weight, the average daily intake was 46 ± 13 kcal/kg for energy and 1.8 ± 0.5 g/kg for protein. Micronutrient intake was in accordance with recommendations for healthy individuals, with the exception of calcium (560 ± 284 mg/d).[14]

Table 3. Composition of Oral Supplements.

Substance	Centrum	Supplement Provided by the Brazilian Public Health System
Retinol, μg	1500	—
Ascorbic acid, mg	60	—
Calciferol, μg	10	—
Tocopherol, mg	30	—
Phytonadione, μg	25	—
Thiamine, mg	1.5	4
Riboflavin, mg	1.7	2
Niacin, mg	20	10
Pyridoxine, mg	2	1
Folic acid, μg	400	5000
Cobalamin, μg	6	—
Pantothenic acid, mg	10	2
Biotin, μg	30	—
Boron, μg	150	—
Calcium, mg	162	500
Chlorine, mg	72	—
Copper, μg	2000	—
Chromium, μg	120	—
Tin, μg	10	—
Iron, mg	18	40
Phosphorus, mg	109	—
Iodine, μg	150	—
Magnesium, mg	100	—
Manganese, mg	2	—
Molybdenum, μg	75	—
Nickel, μg	5	—
Potassium, mg	80	—
Selenium, μg	20	—
Silicon, mg	2	—
Vanadium, μg	10	—
Zinc, mg	15	—

Dashes represent that the supplement does not contain the indicated substance.

Patients regularly used 9 ± 2 drugs/d, consisting of their vitamin and mineral tablets and other drugs. Regarding adherence to drug therapy, only 20% of patients had a low adherence to treatment, 40% of them presented an intermediate adherence, and 40% had high adherence. Regarding their socioeconomic characteristics, 80% of the patients had a low income and a low education level.

Considering the reference values for laboratory data about clinical and nutrition status, patients with SBS presented low serum levels of serum albumin, hemoglobin, and transferrin, whereas CRP was high (Table 4).

All patients had normal serum levels of folic acid and vitamin B_{12}, regardless of the study phase. There was no

Table 4. Clinical and Nutrition Laboratory Data in PN-Dependent Patients With SBS.

	Mean ± SD	Median	Range	Reference Range
Blood glucose, mg/dL	82 ± 15	84	65–114	70–100
Urea, mg/dL	41 ± 24	42	15–91	10–50
Creatinine, mg/dL	1.2 ± 0.4	1.2	0.7–1.8	0.7–1.5
AST, U/L	31 ± 19	28	12–79	<38
ALT, U/L	30 ± 20	24	10–72	<41
GGT, U/L	55 ± 30	49	21–101	5–85
Hemoglobin, g/dL	11 ± 2	11	7.8–13	M:13.5–17.5/F: 12–15.5
Lymphocytes, $10^3/mm^3$	1710 ± 719	1500	900–3000	>1000
Total proteins, g/dL	6.3 ± 1.1	6.1	4.7–8.5	6.4–8.2
Serum albumin, g/dL	3.8 ± 0.5	3.8	3.1–4.8	3.5–5.0
Transferrin, mg/dL	149 ± 57	135	77–228	250–310
C-reactive protein, mg/dL	2.9 ± 3.8	0.9	0.1–10	≤0.5
Ferritin, ng/mL	443 ± 380	508	27–830	M:28–397/F:6–159

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; PN, parenteral nutrition; SBS, short bowel syndrome.

statistically significant difference in folic acid serum levels (15 [6-73] vs 17 [5-110] ng/mL) and vitamin B_{12} (716 ± 277 vs 584 ± 226 pg/mL) in phases 1 and 2, respectively. There was no statistically significant difference in serum levels of vitamins A and C between the phases of the study, whereas the values of vitamin E were reduced between phases 1 and 2 (Table 5).

Correlation between oral intake of vitamins A, C, and E and their respective serum levels was not observed, regardless of the study phase. Except for the association between the time of intestinal resection and serum levels of vitamin E ($r = 0.64$, $P = .04$), there was no correlation between the levels of other vitamins and age, BMI, time of intestinal resection, and remaining intestine length.

Discussion

In the present study, the PN cycle's vitamin and home oral vitamin supplementation was not enough to make the serum levels of vitamins A, C, and E reach normal serum values. After the period in which patients stayed at home, vitamins A and C remained at similarly low serum levels, whereas vitamin E serum level concentration decreased. Most patients seemed to be adherent to drug treatment and presented an appropriate pattern of food intake. However, an increase in the oral amount of vitamin does not necessarily correspond to an increase in serum level.

In this study, patients with SBS presented vitamin A serum levels lower than the reference range, even after PN, and these values remained low during the period they stayed at home. Contrary to the present result, hypovitaminosis A is not commonly described in patients with SBS. Hypovitaminosis A has occurred only in 20%[15] and 5%[16] of PN-dependent patients with SBS.

In the current study, most patients presented low serum vitamin C, even after PN. The vitamin C serum levels did not vary significantly during the period that patients were at home. These results are consistent with previous studies on vitamin C in patients receiving PN.[9,17] Hypovitaminosis C has been documented in 15%[18] to 33%[19] of patients receiving PN at home and also has been shown in patients receiving PN with an adequate supply of vitamin C.[20] Based on the clinical status of the present study patients, it is possible that they had a metabolic consumption of C vitamin, probably due to oxidative stress.[21,22] The amount of vitamin C recommended for PN-dependent patients with SBS is questionable, considering the benefit of higher doses of vitamin C and urinary oxalate excretion[23,24] and nephrolithiasis.[25]

Considering the reference values, vitamin E serum levels from this study were low, especially after the period when patients stayed at home. Lower values of vitamin E have also been documented in home PN patients for longer periods of time.[26,27] The occurrence of hypovitaminosis E in patients undergoing PN ranges from 17% to 100%.[9,16] It is possible that the variation in the results may be due to the conditions of remaining intestine and time on PN.

Even though the total amount of oral vitamins provided by diet and medication seemed to be adequate for an individual with an intact intestine, this was not enough to raise serum levels of vitamins in PN-dependent patients with SBS while they were at home. The interpatient differences regarding location, functionality and extent of the remaining intestine, presence of the ileocecal valve, patient's age, adaptive ability, and treatment instituted should be taken into account individually.[3,28,29]

Vitamin absorption from food has not been determined but was estimated according to patients' diet records processed by specific software (NutWin 1.5 Professional Software). We intend to develop methods with vitamins marked with stable isotopes to evaluate their absorption. At the moment, though, we still do not have this technique available in our laboratory.

Table 5. Total Amount of Vitamins Received by Oral Route and Serum Levels of Vitamins A, C, and E in Phases 1 and 2 of PN-Dependent Patients With SBS.

	Vitamin A			Vitamin C			Vitamin E		
SBS Patients	Quantity Supplied, mg/d	Serum Level, µmol/L (Reference Range 1.04–2.43)		Quantity Supplied, mg/d	Serum Level, mg/dL (Reference Range 0.6–2.0)		Quantity Supplied, mg/d	Serum Level, µmol/L[a] (Reference Range 23–27)	
		Phase 1	Phase 2		Phase 1	Phase 2		Phase 1	Phase 2
1	1891	0.61	0.21	74	0.16	0.2	33	25.1	13.6
2	2035	0.55	0.43	311	0.59	0.43	38	38	12.9
3	270	0.6	0.5	1100	0.4	0.19	5	16.5	14.5
4	1991	0.55	0.35	158	0.56	0.24	43	20.7	12.9
5	1860	0.55	0.78	648	0.48	0.41	37	11.9	14.1
6	2029	1.02	0.7	336	0.1	0.2	37	22	18.5
7	367	1.23	1.3	632	0.26	0.79	18	20.5	15.8
8	1683	0.93	0.56	253	0.14	0.02	46	18.2	14.3
9	1747	0.43	1.11	256	0.12	0.1	41	12.4	13.8
10	2101	1.21	1.11	309	0.23	0.14	45	16.4	9.3
Median	1875.5	0.61	0.63	310	0.25	0.2	37.5	19.4	14
Range	270–2101	0.43–1.23	0.21–1.3	74–1100	0.1–0.59	0.02–0.79	5–46	11.9–38	9.3–18.5

Phase 1: immediately after the end of each cycle of PN; phase 2: before the beginning of next cycle of PN. PN, parenteral nutrition; SBS, short bowel syndrome.
[a]$P = .03$ comparison between phases 1 and 2.

Patients with SBS are constantly exposed to situations that cause oxidative stress, such as infection,[2,30] presence of a totally implanted catheter,[31] and even the infusion of PN with lipids.[26,27] This situation of oxidative stress could explain a higher consumption of antioxidant agents such as vitamins C and E.[32] The evaluation of vitamin serum levels only may not be an effective marker of vitamin status.

Serum concentrations of folic acid could be best assessed by erythrocyte folate.[33] Determination of vitamin B_{12} serum levels may not be an adequate marker to evaluate its deficiency[34] because even in the absence of low serum levels, the patient may present functional deficiency of this vitamin.[33] Vitamin B_{12} deficiency may have a late diagnostic due to subclinical manifestations and the lack of accurate information on the remaining intestinal segment; furthermore, this vitamin deficiency could be better diagnosed when there are elevated serum levels of methylmalonic acid and homocysteine.[34]

In this study, even though the laboratory deficiency of vitamin A was documented, no specific tests were performed to assess visual acuity, which could be a suggestion for future studies with patients with SBS. Although serum levels of ascorbic acid lower than 0.3 mg/dL indicate an inadequate supply of vitamin C, further investigation should be conducted to determine the cell concentration, mainly leukocytes.[20]

Although the number of patients enrolled in this study was small, it represented the totality of patients with SBS attended during this research. SBS has a low prevalence in the world population, and many publications are case reports. Even in investigations documenting larger samples, the number of patients is reduced and similar to the current study population. The institution where this research was conducted is a public referral teaching hospital. For this reason, all patients were referred from hospitals in other cities to this regional reference hospital. Consequently, all patients underwent bowel resection in other places and were referred, after a few months, to be assisted at the present institution.

In the current study, the total oral amount of vitamins patients were receiving did not seem to be enough to normalize the serum levels up to the reference value. Because of this, supplementation with higher doses of those vitamins should be investigated, taking into consideration their solubility. According to what has been suggested in other studies, supplementation with higher doses of those vitamins should be investigated, as well as supplementation with water-soluble forms, particularly for vitamin E.

Regarding the laboratory data about clinical and nutrition status (Table 4), although all patients were clinically and hemodynamically stable during the process of sample collection, it is possible that they had some degree of dehydration in phase 2, which could have hemoconcentrated the blood samples, resulting in a false-negative result, since vitamin serum-level deficiencies were evaluated in this study.

In this study, although clinical manifestations of infection were not detected in patients with SBS, some of them presented persistent and elevated levels of CRP and ferritin. It is possible that these alterations could suggest that an acute phase

response of the inflammatory process took place in these patients,[35] which could be related to the presence of a totally implanted catheter, biofilm formation, microorganism adherence to the central venous catheter used for PN administration, and even the infusion of PN with lipids.[26,27,31]

At the present institution, patients were considered able to receive PN only if they were clinically and hemodynamically stable. In the absence of other abnormalities, the increase of CRP and ferritin did not contraindicate the administration of a new PN cycle.

In conclusion, it was possible to verify that patients were not receiving an adequate vitamin supplementation through the digestive route by means of food and oral vitamin supplements. The supply of vitamins through PN was not enough to raise levels of vitamins A, C, and E up to the normal range during the period of hospitalization. Further studies must be conducted to investigate vitamin supplementation in higher doses, whether through oral or intravenous administration, and assessing differences between water and liposoluble forms of supplementation.

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