Nutrition 27 (2011) 435–439

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Vitamin C supplementation in patients receiving peripheral parenteral nutrition after gastrointestinal surgery

Eriko Yamazaki M.D., Masahiro Horikawa M.D., Ryoji Fukushima M.D., Ph.D. *

Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 20 July 2009
Accepted 28 February 2010

Keywords:
Postsurgery
Ascorbic acid
8-Isoprostane
Surgical stress
Oxidative stress

ABSTRACT

Objective: We investigated an adequate vitamin C dose during peripheral parenteral nutrition therapy in patients after gastrointestinal surgery by measuring blood concentrations and urine excretions of vitamin C. We also sought to identify the effects of vitamin C on the oxidative status.
Methods: In a randomized trial, 2 d after undergoing gastrointestinal surgery, 16 patients started to receive a 5-d continuous intravenous infusion of vitamin C, either 100 or 500 mg/d. Blood concentrations of vitamin C and inflammatory and immunologic parameters were measured preoperatively, the day after surgery, and 3 and 5 d after starting administration of vitamin C (day 3 and day 5). Also, excretions of vitamin C and oxidative stress markers in 24-h, cumulative urine samples, collected and stored under light protection at 0°C, were measured on day 3 and day 5.
Results: Mean blood vitamin C concentration decreased markedly after surgery. The concentration returned to normal on day 3 and on day 5 in the 500-mg group and only on day 5 in the 100-mg group. Concentrations differed significantly between the groups on day 3 and on day 5 ($P < 0.001$ for both days). Urinary vitamin C excretion was above normal on both days in the 500-mg group, but it never reached normal in the 100-mg group ($P < 0.001$ for both days). Urinary excretion of 8-isoprostane, a marker of oxidative stress, was significantly lower in the 500-mg than in the 100-mg group on day 3 ($P = 0.002$).
Conclusion: Vitamin C dose of 500 mg/d, not 100 mg/d, is adequate for patients undergoing gastrointestinal surgery and receiving peripheral parenteral nutrition therapy. Vitamin C may decrease postsurgical oxidative stress.

Introduction

Parenteral nutrition therapy is commonly used to treat patients who cannot receive enteral nutrition or who cannot receive it in sufficient amounts after gastrointestinal surgery. Peripheral parenteral nutrition (PPN) therapy, but not total parenteral nutrition (TPN) therapy, is used in some countries, mainly for short periods after surgery until the gut can tolerate oral nutrition [1–3].

The regulatory requirements for supplemental vitamins administered during parenteral nutrition in Japan differ greatly between TPN and PPN therapy. Vitamin supplementation is essential during TPN therapy, and TPN solutions preformulated with multivitamins, packaged in multichamber containers, are widely used. On the other hand, supplemental vitamins are not always used during PPN therapy because the period of therapy is short (typically a few days), oral feeding is often permitted, and the benefits of vitamin administration and the risks of vitamin deficiency have not been established [3,4].

In a previous study, we investigated the water-soluble vitamin status after gastrointestinal surgery by measuring blood concentrations and urinary excretions of vitamins B_2, B_6, B_{12}, and C [4]. In that study, we found that the nutritional status of these vitamins, except for vitamin B_{12}, became worse during short-term PPN therapy without vitamin supplementation. In particular, vitamin C status markedly decreased in all patients throughout the study. Therefore, vitamin C levels were considered to be deficient during short-term PPN without supplementation.

The results mentioned above may be due to an increase in vitamin C requirements caused by surgical stress. Because vitamin C has an anti-oxidative effect [5], the deficiency of this vitamin may increase the level of oxidative stress, which may increase the risk of postoperative complications and may cause delayed recovery from surgical insults. Recent studies have

* Corresponding author. Tel.: ++81-3-3963-1231; fax: ++81-3-5375-6097.
E-mail address: ryojif@med.teikyo-u.ac.jp (R. Fukushima).

0899-9007/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.nut.2010.02.015

also shown that vitamin C requirements do increase in surgical and trauma patients [6–8], and clinical outcomes of surgical patients are adversely affected by vitamin C deficiency to cause, for example, hemorrhage, anemia [9], and ecchymosis [10]. These signs are reported to have disappeared after an administration of vitamin C. Despite these clinical observations, the appropriate dose of the vitamin C and its effects on the oxidative stress have not been sufficiently understood.

In the present study, we investigated the adequacy of two vitamin C doses in patients receiving PPN after gastrointestinal surgery as well as the effects of vitamin C administration on the oxidative stress. The dose of 100 mg/d meets the American Medical Association's 1975 recommendation [11] for parenteral supplementation, and the dose of 500 mg is the maximum dose of commercially available vitamin preparations in Japan.

Patients and methods

Patients

Patients admitted in Teikyo University Hospital between October 2008 and January 2009, who were scheduled to undergo gastrectomy or colorectal resection and who would require PPN therapy after surgery, were enrolled. All patients were 20 y old or older and could give written informed consent. Exclusion criteria included the followings: 1) abnormal electrolyte metabolism; 2) congestive heart failure; 3) serious liver failure (with hepatic coma or possible hepatic coma); 4) serious kidney failure or azotemia; 5) abnormal amino acid metabolism; 6) severe acidosis; 7) occlusive uropathy that decreased urine volume; 8) a history of hypersensitivity to the ingredients of the PPN solution; 9) other reasons as determined by the investigators.

The present study was approved by the Ethics Committee of the Teikyo University School of Medicine and was conducted in accordance with the ethical principles of the Helsinki Declaration. Written informed consent for participation was obtained from each patient before enrollment in the study.

Procedure

The study was a randomized clinical trial using a permuted block design. Eligible patients were assigned to either the 100-mg group or the 500-mg group. Commercial PPN solutions generally used after surgery, such as maintenance solutions containing carbohydrates, amino acids, and electrolytes, were administered continuously at the target dose of 2000 mL/d. Vitamin C (100 mg or 500 mg, depending on the study group) was diluted to 48 mL physiologic saline and continuously administered intravenously for 5 d by an infusion pump at a rate of 2 mL/h, beginning 2 d after and continuing through 7 d after surgery.

Blood concentrations of vitamin C and inflammatory and immunologic parameters were measured preoperatively, then on the day following surgery (POD 1), and 3 and 5 d after starting administration of vitamin C [defined as day 3 (POD 5) and day 5 (POD 7), respectively]. On days 3 and 5, urinary excretions of vitamin C and concentrations of oxidative stress markers in 24-h, cumulative urine samples, collected and stored under light protection at 0°C, were measured.

Patients were not allowed to receive TPN, enteral nutrition solutions, or other vitamin preparations from the day before surgery until the last data collection time on day 5. Patients were not allowed to receive solid food until after data collection on day 3, but hospital meals were permitted on days 4 and 5. Patients could drink water throughout the study. These restrictions were explained to the patients before the study, and patients adhered to them throughout the study.

Hematology and blood chemistry tests were conducted in the clinical laboratory of Teikyo University Hospital and other measurements were conducted by a contract laboratory. Blood and urine samples were treated and stored according to the procedures determined by Teikyo University Hospital laboratory or by the contract laboratory.

The blood vitamin C levels were measured by high-performance liquid chromatography using the serum sample subjected to deproteinization and subsequent reduction with dithiothreitol [12]. In addition to blood levels of vitamin C and inflammatory and immunologic parameters, C-reactive protein (CRP), white blood cell counts, lymphocyte counts, and neutrophil counts were also measured. These measurements were obtained with standard methods in the laboratory of Teikyo University Hospital. Urine concentrations of vitamin C and two stress markers, 8-isoprostane and 8-Hydroxydeoxyguanosine (8-OHdG), were measured from 24-h cumulative urine samples. The urine was collected in a bottle placed in a light-protected ice box. Then the samples were moved into a small plastic tube; air was excluded and the samples were frozen until analyzed. Urinary concentrations of vitamin C were measured by the dinitrophenylhydrazine method as described elsewhere [13,14]. The concentrations of 8-OHdG and 8-isoprostane were measured by the enzyme immunoassay. The laboratory used an improved sample-pretreatment method to increase the accuracy of the 8-isoprostane measurement [15].

Table 1
Normal reference ranges for blood and urine measurements*

Measurements	Reference range
Blood concentration of vitamin C* (μmol/L)	31.2 to 95.4
Urinary excretion of vitamin C† (mg/d)	>26.4
C-reactive protein‡ (mg/dL)	<0.30
White blood cell count‡ (/μL)	3500 to 8400

The normal reference range is the central 95% of values in distributions obtained from a healthy population.

* From the analytical laboratory that measured the values for this study.

† Established by the research that was conducted to determine the Dietary Reference Intakes for Japanese [16].

‡ From the Teikyo University Hospital laboratory that measured the values for this study.

Normal reference ranges presented by Teikyo University Hospital or the contract laboratory were used to interpret blood test results (Table 1). The normal reference range used here was the central 95% of values in distributions obtained from a healthy population. Normal ranges for 8-isoprostane and 8-OHdG were not available. Urinary excretion of vitamin C was evaluated using the lower limit established by the research that was conducted to determine the Dietary Reference Intakes for Japanese [16]. For both blood concentrations and urine concentrations, if the measured value was below the lower detection limit, the value was determined to be the half of the value of the lower detection limit. Blood concentrations of Na, K, Cl, aspartate aminotransferase, alanine aminotransferase (ALT), blood urea nitrogen, and creatinine were measured by standard methods in the clinical laboratory of Teikyo University Hospital. All measurements were conducted by technicians blinded to group assignment.

Statistical methods

Changes of blood vitamin C concentrations from the value on the day after surgery between groups were analyzed with ANOVA. The differences in the urinary excretion of vitamin C, blood concentrations of inflammatory and immunologic parameters, and urinary excretions of the stress markers between groups were analyzed with the Wilcoxon test. Alpha was set at 0.05, and all tests were two-tailed. The SAS statistical software package (version 9.1.3, SAS Institute Inc. Cary, NC) was used for all analyses.

Results

Patient characteristics

Of the 19 patients (13 men) enrolled in the study, 7 patients in the 500-mg group and 9 patients in the 100-mg group were included in the final analysis (Table 2). All withdrawals were in the 500-mg group. One patient withdrew from the trial because the patient did not receive the operation. One discontinued because of the patient's refusal during the postoperative period. One was discontinued because of insufficient urine collection. All surgeries were uncomplicated and uneventful.

The average (SD) amount of solution administered during the study was 2389 (269) mL/d in the 100-mg group and 2224 (243) mL/d in the 500-mg group. Although hospital food was permitted after day 3, no patient actually ate any solid food or took oral supplements or additional vitamins throughout the study. Therefore, only the vitamin C administered with the PPN solution could have affected vitamin C status.

Measurements of vitamin C

Mean blood vitamin C concentrations were within the reference range before surgery but were below the range on the day after surgery in both groups. In the 500-mg group, the mean value recovered to the reference range on both day 3 and day 5. However, in the 100-mg group, the value was still below the