Clinical Examination of the Water-Soluble Vitamin Levels in Blood during Peripheral Parenteral Nutrition

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Received 15 September 2006, accepted 5 December 2006

Summary: The water-soluble vitamin (included vitamin B1, B6, B12 and C) preparations are not always replenished when peripheral parenteral nutrition (PPN) is used in Japan. We evaluated the need for administration of vitamins preparation during PPN, and involved analysis of the blood levels of water-soluble vitamins in patients receiving perioperative PPN before and after gastrectomy. Patients were examined as two set of groups as follows; 18 patients who did not receive water-soluble vitamin preparations during PPN, the Unsupplemented Group, and 22 patients who received such preparations during PPN, the Supplemented Group. Consequently, in the Unsupplemented Group, the blood vitamin B1 level during the early postoperative period was significantly lower than the preoperative level, but in the Supplemented Group, it was significantly higher than the preoperative level. In the Supplemented Group, the blood vitamin B12 level during the early postoperative period was markedly higher than the preoperative level. And in both groups, the blood vitamin C level remained below the lower limit of the criterion range throughout the perioperative period. These results suggested that administration of water-soluble vitamins during PPN was needed to avoid potential vitamin deficiencies after surgery and to prevent a potential onset of severe metabolic complications from any deficiencies.

Key words water-soluble vitamin, peripheral parenteral nutrition (PPN), micronutrient

INTRODUCTION

Recent advances in parenteral and enteral alimentation have contributed to improving the nutrition state of patients. For example, total parenteral nutrition (TPN), which was developed in 1967 by Dudrick et al. [1], has been used extensively as a means of nutrition for patients who are unable to receive peroral ingestion or enteral nutrition, or who can do so only with difficulty. However, TPN have resulted in progressively larger number of patients with metabolic complications [2-3], such as vitamin B1 deficiency

(Wernicke encephalopathy, lactic acidosis, etc.) and other complications of deficiencies in micronutrients (vitamins, trace elements, etc.) [4-10]. For this reason, the guideline prepared by the American Society for Parenteral and Enteral Nutrition (ASPEN) have recommended that care should be taken to ensure intake of these elements in the amounts needed daily by patients receiving nutrition with this method [11].

Peripheral parenteral nutrition (PPN) is simpler and cost less than TPN. Because of these features, PPN is often used to provide nutrients. PPN involves administration of lower amounts of carbohydrates

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Abbreviations: BMI, body mass index; CLEIA, chemiluminescent enzyme immunoassay; DG, distal gastrectomy; GIST, gastrointestinal stromal tumor; HPLC, high performance liquid chromatography; IRB, institutional review board; LAPG, laparoscopic-assisted partial gastrectomy; PG, partial gastrectomy; PPG, pylorus preserving gastrectomy; PPN, peripheral parenteral nutrition; SG, segmental gastrectomy; TPN, total parenteral nutrition.

and its duration is short (about 1-2 weeks) [12], so that deficiency of micronutrients is considered unlikely to occur with this method. As a result, vitamins are not always prescribed when PPN is used in Japan. Although the guidelines mentioned above recommendation that adequate care should be taken to ensure intake of the required amounts of vitamins every day when parenteral nutrition is used, the optimal dosage and method of administration of micronutrients during PPN are still unclear. Furthermore, although administration of vitamins during the perioperative period is considered preferable because of their antioxidative effects and the involvement of vitamins in glucose and protein metabolism, no detailed criteria are available for dosages or method of administration of vitamins during this period. Moreover, under the current health insurance system in Japan, reimbursement for concomitant use of water-soluble vitamin preparations is limited during PPN. In these circumstances, not a little cases of severe metabolic disease developing during PPN due to vitamin B1 deficiency have been reported [13-14], resembling those previously reported in association with use of TPN. These reports have been suggesting that patients with certain diseases might be suffered potential vitamin deficiency.

The aims of this study were to examine the need for administration of water-soluble vitamin preparations during PPN, and involved analysis of the blood levels of water-soluble vitamins (B1, B6, B12 and C) in patients receiving perioperative PPN before and after gastrectomy.

SUBJECTS AND METHODS

Subjects

The subjects of this study were patients who were scheduled to receive PPN after gastrectomy, at the Department of Surgery of Kurume University Hospital. During the period from April 2003 to September 2005, 40 patients were enrolled in this study, including 18 patients who received no water-soluble vitamin preparations during PPN-the Unsupplemented Group, and 22 patients who received such preparations during PPN-the Supplemented Group.

Prior to the start of the study, all candidates were informed of the study design, and their consent to participate in the study was obtained in writing. (For candidates incompetent to provide consent, consent was obtained from their guardians.) Institutional

review board (IRB)-No.2258 for the Unsupplemented Group was approved at 16th Dec. 2002 by IRB for Kurume University School of Medicine. On the other side, we thought that blood sampling and measurement of blood vitamin levels for the Supplemented Group are one of the common practice act. Therefore, we did not ask for IRB's approval as to these act.

All patients enrolled in this study satisfied all of the following requirements [1] in good general condition and able to ingest food and drink before surgery; [2] with no severe medical complication before surgery; [3] scheduled to receive PPN after surgery; and [4] providing informed consent to participate in the study in writing, accompanied by written consent of their attending physicians.

Additionally the following exclusion criteria were applied; [1] severe hepatic, renal, or cardiac dysfunction; [2] severe abnormality in glucose metabolism; [3] hyperkalemia associated with Addison's disease, severe burns, or azotemia; [4] hyperphosphatemia associated with hypoparathyroidism; [5] hypermagnesemia associated with hypothyroidism; [6] hypercalcemia; and [7] any clear sign of vitamin deficiency.

Experimental protocol (Fig. 1)

For both the Supplemented and Unsupplemented groups, PPN was performed using multiple electrolyte injection with carbohydrate (electrolyte maintenance solution or extracellular fluid replacement

Fig. 1. Experimental protocol. PPN was performed using multiple electrolyte injection with carbohydrate (MEIC) or amino acid injection with glucose (AAIG). Administration of the water-soluble vitamin preparation was discontinued when oral ingestion was resumed after surgery. PPN was gradually changed to oral ingestion. For each patient, blood was sampled at 3 time points, i.e., preoperative period ("Pre"), early postoperative period ("EPP"), and late postoperative period ("LPP").

solution) or amino acid injection with glucose. After surgery, the volume of IV solution administered was increased or decreased appropriately depending on the condition of each patient, with a target of 30-40 ml/kg/day. The water-soluble vitamin preparations used for the Supplemented Group included vitamin B1 (50 mg/day as thiamine disulfide), vitamin B6 (100 mg/day as pyridoxine hydrochloride), vitamin B12 (1 mg/day as hydroxocobalamin acetate), and vitamin C (500 mg/day). These preparations were used to prescribe to the patients who were underwent gastrectomy in our hospital. The water-soluble vitamin preparations were administered together with the initial 500 ml of the IV fluid used for each day over a period of around 5-6 hrs, while covered and shielded from the light. Administration of the water-soluble vitamin preparations were discontinued when peroral ingestion was resumed after surgery. The amount of PPN was gradually reduced and peroral ingestion was started. Peroral ingestion was started at around 3 days after surgery when judged feasible by the attending physician. The diets which usually administered to gastrectomized patients at our hospital were used. Peroral ingestion was started with 30% rice gruel, followed by 50% rice gruel, and then by 100% rice gruel, at intervals of 2 days. After peroral ingestion had reached 100% rice intake, the patient was discharged from the hospital.

For each patient, ten milliliters of blood was sampled at 3 time points, i.e., preoperatively (Pre.), at immediately before the start of peroral ingestion after surgery (early postoperative period; EPP), and at around 6 days after the start of peroral ingestion (late postoperative period; LPP). At each time point, blood was collected early in the morning before breakfast.

Methods of measurement of water-soluble vitamin levels in blood

Blood vitamin B1, B6, and C levels were measured using high-performance liquid chromatography post-column fluorescence method (HPLC). Vitamin B12 was measured with chemiluminescent enzyme immunoassay (CLEIA). Both methods have been recommended by the Vitamin Society of Japan [15].

This study is a pilot study not a double-blind study. For comparisons between two groups, ANOVA was used, followed by testing of the significance of differences with Fisher's PLSD, and between the preoperative and postoperative period, Student's t-test was used. In all analyses, findings of $p < 0.05$ were considered significant.

Patients for whom a given parameter was above

the lower limit of the criterion range were considered that the vitamin sufficiency was "maintained patients", while those for whom the parameter was less than the lower limit of the criterion range were considered "non-maintained patients". The rate of maintenance for each vitamin was calculated using the following equation:

$$\text{Maintenance rate (\%)} = \frac{\text{maintained patients}}{(\text{maintained patients} + \text{non-maintained patients})} \times 100$$

Fisher's exact method was employed for comparisons of this parameter between the two groups (excluding patients for whom blood sampling had not been performed).

RESULTS

Background of the patients

In the Unsupplemented Group, there were 13 males and 5 females, with a mean age of 66.9 ± 2.9 years (mean $\pm$ SEM). The average body mass index (BMI) was 22.8 ± 0.9 . The primary diseases were gastric cancer in 15 cases (Stage I A in 14 cases, and Stage I B in 1 case) [16], and gastric gastrointestinal stromal tumor (GIST) in 3 cases. The operative procedures were distal gastrectomy in 12 cases (reconstruction with Billroth-I procedure in 10 cases, and Roux-en-Y reconstruction in 2 cases), pylorus-preserving gastrectomy in 2 cases, partial gastrectomy in 3 cases (open surgery in 1 case, and laparoscopic surgery in 2 cases), and segmental gastrectomy in the other 1 case.

In the Supplemented Group, there were 12 males and 10 females, with a mean age of 66.9 ± 2.3 years (mean $\pm$ SEM). The average BMI was 22.2 ± 0.6 . The primary diseases were gastric cancer in 21 cases (Stage I A in 15 cases, Stage I B in 3 cases, Stage II in 2 cases, and Stage III A in 1 case) [16], and gastric GIST in 1 case. The operative procedures were distal gastrectomy in 19 cases (reconstruction with Billroth-I procedure in 10 cases, Billroth-II procedure in 2 cases, and Roux-en-Y reconstruction in 7 cases), pylorus-preserving gastrectomy in 1 case, open partial gastrectomy in 1 case, and segmental gastrectomy in the other 1 case. In the male-to-female ratio, age, primary disease, stage of disease, and operative procedure, there was no significant difference between the two groups.

Parenteral nutrition during fasting period

The mean postoperative period of fasting was

3.5 ± 0.3 days in the Unsupplemented Group, 4.1 ± 0.1 days in the Supplemented Group. The mean amount of infusion volume and mean daily caloric intake during this period were 2100.5 ± 85.7 ml, 549.7 ± 30.9 kcal (non-protein calorie intake was 459.7 ± 24.0 kcal) in the Unsupplemented Group, 2006.8 ± 12.4 ml, 428.6 ± 19.2 kcal (non-protein calorie intake was 398.6 ± 9.4 kcal) in the Supplemented Group, respectively.

Nutrition after resumption of peroral ingestion

The mean length of time from the start of peroral ingestion to LPP blood sampling was 4.6 ± 0.3 days in the Unsupplemented Group, and was 7.2 ± 0.3 days in the Supplemented Group. From the start of peroral ingestion till LPP blood sampling, the mean daily caloric intake, the mean daily protein intake were 1027.7 ± 0.4 kcal, 39.8 g in the Unsupplemented Group, and were 1031.0 ± 0.3 kcal, 39.7 g in the Supplemented Group. Also the mean daily intake of vitamin B1, B6, B12, C were 3.30 mg, 4.5 mg, 6.5 μ g, 277 mg in the Unsupplemented Group, and were

3.30 mg, 4.7 mg, 6.4 μ g, 278 mg in the Supplemented Group.

Changes of each blood vitamin levels

Vitamin B1 (the criterion range; 28 to 56 ng/ml) [17]

In the Unsupplemented Group, the blood vitamin B1 level at the EPP (26.1 ± 2.1 ng/ml) was significantly lower than the preoperative level (30.9 ± 1.6 ng/ml), and did not recover adequately even at the LPP (27.0 ± 1.5 ng/ml). In the Supplemented Group, the blood vitamin B1 level at the EPP (172.8 ± 12.3 ng/ml) was significantly higher than the preoperative level (41.0 ± 4.1 ng/ml), and decreased to 57.9 ± 13.5 ng/ml at the LPP (Fig. 2a).

Vitamin B6 (the criterion range; male: 6 to 40 ng/ml, female: 4 to 19 ng/ml) [18]

In the Supplemented Group, the blood vitamin B6 level at the EPP (38.8 ± 2.8 ng/ml) was significantly higher than the preoperative level (13.3 ± 3.9 ng/ml), and decreased to 16.2 ± 2.6 ng/ml (close to the preoperative level) at the LPP (Fig. 3a).

Fig. 2. Changes and Maintenance rate in the blood vitamin B1 levels.

pre: preoperative period, EPP: early postoperative period, LPP: late postoperative period

(a) In the Unsupplemented Group, blood vitamin B1 level at the EPP was significantly lower than the preoperative level ($p < 0.01$), and in the Supplemented Group, it was significantly higher than the preoperative level ($p < 0.01$).

(b) The rate of maintenance of blood vitamin B1 at the EPP and LPP was both 100% in the Supplemented Group, but in the Unsupplemented Group was 21.4% and 37.5%.

Fig. 3. Changes and Maintenance rate in the blood vitamin B6 levels.

pre: preoperative period, EPP: early postoperative period, LPP: late postoperative period

(a) In the Supplemented Group, blood vitamin B6 level at the EPP was significantly higher than the preoperative level ($p < 0.01$).

(b) The rate of maintenance of blood vitamin B6 at the EPP and LPP was both high in the Supplemented Group, but in the Unsupplemented Group was 28.6% and 37.5%.

Fig. 4. Changes and Maintenance rate in the blood vitamin B12 levels.

pre: preoperative period, EPP: early postoperative period, LPP: late postoperative period

(a) In the Supplemented Group, blood vitamin B12 level at the EPP was markedly higher than the preoperative level ($p < 0.01$), and remained high even at the LPP.

(b) There were no significant differences between the two groups in rate of maintenance of blood vitamin B12 at the EPP or LPP.

Fig. 5. Changes and Maintenance rate in the blood vitamin C levels.

pre: preoperative period, EPP: early postoperative period, LPP: late postoperative period

- (a) In the Unsupplemented Group, blood vitamin C level at the EPP was significantly lower than the preoperative level ($p < 0.01$) and did not recover adequately even at the LPP. In both groups, blood vitamin C level remained below the lower limit of the criterion range throughout the perioperative period.
- (b) The rate of maintenance of blood vitamin C did not differ significantly between the two groups at the EPP or LPP, and remained very low in both groups.

Vitamin B12 (the criterion range; 233 to 914 pg/ml) [18]

In the Supplemented Group, the blood vitamin B12 level at the EPP (17781.4 ± 5310.0 pg/ml) was markedly higher than the preoperative level (607.3 ± 114.1 pg/ml), and this remained high even at the LPP (7423.5 ± 3323.5 pg/ml) (Fig. 4a).

Vitamin C (the criterion range; 7.0 to 13.8 µg/ml) [18]

In the Unsupplemented Group, the blood vitamin C level at the EPP (2.0 ± 0.4 µg/ml) was significantly lower than the preoperative level (5.2 ± 0.7 µg/ml), and did not increase at the LPP (3.3 ± 0.6 µg/ml). In the Supplemented Group, the blood vitamin C level remained fairly constant throughout the perioperative period. In both groups, the blood vitamin C level remained below the lower limit of the criterion range throughout the perioperative period (Fig. 5a).

Maintenance rate of each blood vitamin levels (Figs. 2b-5b)

The rate of maintenance of blood vitamin B1 level, B6 level at the EPP were 100% (22/22), 100% (22/22) in the Supplemented Group, and were 21.4% (3/14), 28.6% (4/14) in the Unsupplemented Group, respectively. Both blood vitamin B1 and B6 levels were maintained significantly better in the Supplemented Group than in the Unsupplemented Group at the EPP. At the LPP, the rate of maintenance of blood vitamin B1 level, B6 level were 100% (20/20), 95% (19/20) in the Supplemented Group, and were 37.5% (6/16), 37.5% (6/16) in the Unsupplemented Group, respectively. Thus, both blood vitamin B1 and B6 levels were maintained significantly better in the Supplemented Group than in the Unsupplemented Group, at the LPP. There was no significant difference between the two groups in the rate of maintenance of blood vitamin B12 at the EPP and LPP. The rate of maintenance of blood vitamin C did not differ significantly between the two

groups at the EPP nor LPP, and remained very low in both groups.

DISCUSSION

TPN is associated with problems such as metabolic acidosis and Wernicke encephalopathy, and other severe complications of micronutrient deficiency [4-10]. At present, it is therefore recommended that TPN should be accompanied by vitamin administration [11].

Regarding the need for vitamin administration during PPN, it has been believed that severe complications of vitamin deficiency are unlikely to occur since the amounts of calories and of carbohydrates administered are small during PPN and because the duration of PPN is usually short [12]. In this study, however, it was demonstrated that the blood vitamin B1 level about 3 days of PPN in about 79% of the patients who received PPN throughout the perioperative period without vitamin administration was below the lower limit (28 ng/mL) of the criterion range proposed by the Committee for Vitamin Laboratory Standards, Japan [17]. In about 71% of the same perioperative patients receiving PPN without vitamin administration, the blood vitamin B6 level was below the lower limit of the criterion range, and all of these patients also had blood vitamin C levels below the lower limit of the criterion range. Prior to the present study, there have been reported that about 20-40% of patients admitted to a critical care unit or patients who had undergone gastrointestinal surgery already had a very low blood vitamin B1 level before the start of PPN, and that their blood vitamin B1 level decreased further after PPN without vitamin administration [18-19]. Shineha et al. [21] and Goseki and Tsuchiya [22] had also reported that 40-60% patients who had received gastrointestinal surgery had shown less than 28 mg/ml of blood vitamin B1 level after PPN. These findings suggested that PPN without vitamin administration in patients after gastrointestinal surgery could likely cause vitamin B1 deficiency.

It was reported that total body vitamin B1 depletion can occur within eighteen days [23], and deficiency in vitamin B1 occurs earlier than deficiency in any other vitamin if vitamin intake is stopped [24]. Vitamin B1 deficiency presents very severe complications such as lactic acidosis and Wernicke encephalopathy, and the number of patients with these complications has not decreased in recent years [4-10,25]. Thus, among patients with various primary diseases, some are malnourished and poten-

tially prone to vitamin deficiency.

From the point of view of prevention vitamin B1 deficiency, preparations for PPN supplemented with vitamin B1 have been developed recently. These preparations are expected to be very useful and safety. It has been reported that the use of these preparations during the period of fasting after gastrointestinal surgery enabled good maintenance of blood vitamin B1 level [21-22]. It has also been reported that in patients with shock or critically ill, loss of vitamin B increased, resulting in rapid onset of symptoms of vitamin B1 deficiency [26]. In patients after gastrointestinal surgery, fasting and stress increased metabolic rate, probably resulting in increased need for vitamins. Compared to previous studies [21-22], this study involved administration of large amounts of vitamin B1 over a short period of time. Although in the Supplemented Group, the blood vitamin B1 level was kept high, we cannot rule out the possibility that the vitamin B1 dosage was a little too much. In any event, it is noteworthy that discontinuation in supplement of vitamin after resumption of oral ingestion resulted in very rapid decrease in blood vitamin B1 level. Furthermore, in the Unsupplemented Group, the percentage of patients in whom the blood vitamin B1 level was kept above the lower limit of the criterion range at the postoperative fasted period was less than 25%, while after resumption of oral ingestion this rate was still less than 40%. The mean blood vitamin B1 was thus less than the lower limit of the criterion range in both the EPP and the LPP. These findings confirmed that vitamin B1 has a very short half-life in blood, and that its blood level decreases rapidly in the absence of vitamin B1 supplementation, and the blood vitamin B1 level does not recover rapidly even after resumption of peroral ingestion. It thus appears essential to administer vitamin B1 during postoperative PPN.

In addition to vitamin B1, three other water-soluble vitamins (B6, B12, and C) were examined in this study.

The rate of maintenance of blood vitamin B6 level was significantly lower in the Unsupplemented Group than in the Supplemented Group, throughout the perioperative period. In the Supplemented Group, the blood vitamin B6 level began to increase soon after surgery, and returned to within the criterion range at the LPP. Although the method used in this study for administration of vitamin B6 may have involved an excessive administration of vitamin B6, no patient exhibited any adverse side-effect. Vitamin

B6 functions as a coenzyme in the metabolism of glucose and protein. The requirement for vitamin B6 correspondingly appears to increase in the presence of stress. Although this study yielded no evidence directly linking blood vitamin levels with clinical outcome, it may be concluded that administration of vitamin B6 in the amounts needed by a given patient is essential for maintenance of blood vitamin B6 level within the criterion range.

The blood vitamin B12 level in 1 patient of the Unsupplemented Group (n=14) was lower than the criterion range at the postoperative fasting period. In the Supplemented Group (n=22), 16 patients exhibited abnormally high blood vitamin B12 level above the upper limit of detection. This unexpected result might be explained by the following factors: (1) vitamin B12 has a long half-life in blood; and (2) the vitamin B12 dosages administered in this study were much higher than those recommended by the guidelines prepared by the American Medical Association (AMA) [27]. The method and dosages of administration of vitamin B12 used in this study appeared likely to show in excessive vitamin B12 blood levels. Further studies are needed to determine the optimal method for administration of vitamin B12 during PPN, however, vitamin B12 supplement dose not seem to be necessary at least for perioperative PPN treatment.

The number of patients in whom the blood vitamin C level was within the criterion range before surgery was small in both the Supplemented Group (2 of 22 patients) and the Unsupplemented Group (5 of 18 patients). During the postoperative parenteral nutrition administration, the blood vitamin C level was below the criterion range in 95-100% of patients in both groups. Since vitamin C plays important roles in collagen cross-linking, is required for wound healing, and reduces the postoperative oxidative stress, it can be considered an essential micronutrient during the perioperative period. Therefore, reduction in vitamin C intake may increase the risk to vitamin C deficiency. In this study, the blood vitamin C level remained below the lower limit of the criterion range, even though once-daily administration of vitamin C was five times of recommended dose. It looks like huge amount of vitamin C might be necessary during perioperative period. Further studies are necessary to determine the dosages and method for administration of vitamin C for perioperative patients.

In this study, the blood vitamin levels were measured using the method recommended by the

Vitamin Standardization Committee [15]. It is still unclear to which extent blood vitamin levels reflect deficiency in vitamins in vivo and whether measurement of blood vitamin levels is clinically beneficial. To answer these questions in detail, it will be necessary to investigate urinary elimination of vitamins and the cellular functions of vitamins. However, for water-soluble vitamins, the reserves of which are very low in vivo and whose half-lives in blood are very short, it seems necessary to keep blood levels within the criterion ranges proposed by the Vitamin Standardization Committee.

Regarding administration of water-soluble vitamins to patients receiving PPN, the guidelines prepared by ASPEN and JSPEN basically recommend that they should be administered in amounts needed by each individual patient [11-12]. From this study, it was shown that the levels of water-soluble vitamins in blood during the brief period of postoperative PPN varied among vitamins. For safer and more effective PPN, the vitamin requirements and optimal methods for administration require further investigation for patients under various conditions. These results might be useful in the planning of such investigations. In conclusion, our studies suggested that administration of water-soluble vitamins during PPN was needed to avoid potential vitamin deficiencies after surgery and to prevent a potential onset of severe metabolic complications from any deficiencies.

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