Poor Prognostic Factors in Patients with Parenteral Nutrition-Dependent Pediatric Intestinal Failure

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Purpose: Parenteral nutrition (PN) not only provides nutritional support but also plays a crucial role in the treatment of children with intestinal failure. The aim of this study was to evaluate the clinical significance and clinical outcomes of long-term PN.

Methods: Retrospective cohort study was conducted using the medical records of patients treated at Seoul National University Children’s Hospital. This study included 19 patients who received PN for over six months. Most patients received home PN.

Results: The indications for PN included short bowel syndrome, chronic intestinal pseudo-obstruction, and intractable diarrhea of infancy. The median age of PN initiation was 1.3 years, and the median treatment duration was 2.9 years. Two patients were weaned from PN; 14 continued to receive PN with enteral feedings; and 3 patients died. The overall survival rates at 2 and 5 years were 93.3% and 84.0%, respectively. The incidence of catheter-related bloodstream infections was 2.7/1,000 catheter-days and was associated with younger age at PN initiation and lower initial height Z-score. Six patients developed catheter-related central vein thrombosis, with an incidence of 0.25/1,000 catheter-days. Eleven patients experienced PN-associated liver disease (PNALD), and one patient underwent multi-visceral transplant. The patients with PNALD exhibited lower final heights and body weight Z-scores. All patients experienced micronutrient deficiencies transiently while receiving PN.

Conclusion: PN is an important and safe treatment for pediatric intestinal failure. PNALD was linked to final anthropometric poor outcomes. Micronutrient deficiencies were common. Anthropometric measurements and micronutrient levels must be monitored for successful PN completion.

Key Words: Parenteral nutrition, Catheter related infections, Cholestasis, Micronutrients
INTRODUCTION

Intestinal failure is characterized by a decreased amount of functional intestine, which is necessary for both proper digestion and absorption, which are required to maintain the appropriate fluid balance and nutrient amounts for the growth of the body [1]. The primary causes of intestinal failure include short bowel syndrome and gastrointestinal functional disorders. Functional disorders may be classified as motility disorders and mucosal diseases. Motility disorders include Hirschsprung’s disease and chronic intestinal pseudoobstruction. Mucosal disorders include microvillous inclusion disease and tufting enteropathy [2].

Long-term parenteral nutrition (PN) therapy is necessary to provide patients with intestinal failure with sufficient body nutrients [3]. Home parenteral nutrition (HPN) is the primary treatment for patients with intestinal failure, as it allows them to live outside the hospital, which improves their quality of life. HPN also improves survival and social functioning and reduces health costs. HPN requires multidisciplinary cooperation among doctors, nurses, pharmacists, clinical dietitians, and psychologists [4,5]. The complications of PN include undernutrition, hyperalimentation, central venous catheter-related infections and thrombosis, cholestasis, and liver disease [6].

PN not only provides nutritional support but also plays a crucial role in the treatment of children with intestinal failure. The aim of this study was to validate both the clinical significance and the clinical outcomes of long-term PN use in patients with chronic pediatric intestinal failure.

MATERIALS AND METHODS

A retrospective study was completed using patients’ medical records in the Department of Pediatrics, Seoul National University Children’s Hospital in Seoul, Korea. The study was performed from July 2001 to June 2014. The Seoul National University Hospital institutional review board approved this retrospective medical record review (IRB No. H-1501-025-639). The present study included 19 simply consecutively recruited patients younger than 18 years of age with chronic intestinal failure who received PN for over six months. Seventeen of these patients received HPN. The current study was performed to investigate and analyze the various factors affecting these patients’ clinical outcomes. These factors included the patients’ ages, genders, diagnoses, ages at PN initiation, PN durations, anthropometric measurements, central catheter types, PN complications, and final outcomes.

Cyclic PN was utilized in all patients providing PN-free intervals ranging from 4 to 12 hours daily. Magnesium sulfate; zinc sulfate; copper sulfate; manganese sulfate; chromium chloride; vitamins A, B1, B2, B3, B6, C, D, E; and selenium were added to the parenteral formulations. Ferric iron, folic acid and vitamin D were supplemented orally if available. The PN compositions were modified to individual needs according to the references [7,8]. The PN was prepared in consultation with a nutritional support team and was mixed using an automated compounding device (MicroMacro Compounder; RS-232, Baxa Corporation, Englewood, CO, USA). Health care professionals provided instruction to HPN caregivers regarding self-care for central lines and the administration of PN during patient hospitalization. After subjects were discharged, home care nurses monitored caregivers’ abilities to manage PN at patients’ homes.

The complications of PN therapy were as follows. Catheter-related bloodstream infections (CRBSIs) were defined as the growth of the same organism from at least one peripheral blood culture and from the removed catheter tip culture. If the catheter was not removed, CRBSIs were defined as growth of the same organism from at least two blood cultures (one from the central catheter and the other from peripheral blood) that met CRBSI criteria for differential time to positivity [9]. Venography is the gold standard method for catheter-related central vein thrombosis diagnosis. However, ultrasonography is the clinically preferred method due to its noninvasi-
veness and accessibility [10,11]. Catheter-related thrombosis was diagnosed via ultrasonography in this study. Parenteral nutrition-associated liver disease (PNALD) was defined by at least two sequential measurements of direct bilirubin >2.0 mg/dL excluding other causes of liver dysfunction [12].

The current study used the lowest micronutrient level during the follow-up period to define micronutrient deficiencies. The normal micronutrient values were as follows: vitamin D, >20 ng/mL; vitamin B, 211-911 pg/mL; folate, >6 ng/mL; copper, 80-155 μg/dL; iron, 50-175 μg/dL; selenium, 75-205 μg/L; magnesium, 1.5-2.3 mg/dL; and zinc, 80-120 μg/dL. Iron deficiency was defined as a serum iron level <50 mg/dL, transferrin saturation <20%, or serum ferritin <30 ng/mL for males and premenarchal females and <15 ng/mL for postmenarchal females [13].

Both initial and final anthropometric indices were measured, including height, weight, and body mass index (BMI). Z-scores were calculated using the modified lambda-mu-sigma (LMS) method, using both the 2006 World Health Organization (WHO) Child Growth Standards and the 2007 WHO Growth Reference.

### Statistical analysis

The data were analyzed using IBM SPSS Statistics version 21 for Windows (IBM Co., Armonk, NY, USA). Fisher’s exact test and a binary logistic regression model were used for the univariate analysis. The odds ratio (OR) and 95% confidence interval (CI) were calculated. A two-sided p-value <0.05 was considered statistically significant. The median values were used as the center values for non-normally distributed data. Nonparametric statistical methods, such as the Mann-Whitney U test and the Wilcoxon signed rank test, were used for non-normally distributed data. Survival curves were obtained using the Kaplan-Meier method. The statistical analysis was reviewed by the Seoul National University Hospital Medical Research Collaborating Center.

### RESULTS

#### Patient characteristics

Nineteen children were recruited for this study (8 were male). The patient characteristics are provided in Table 1. The median age of the patients was 9.9 years, and the median age at PN initiation was 1.3 years; the median duration of PN treatment was 2.9 years. Four patients started PN when they were over 10 years of age. The most commonly used central catheter was the chemoport, which was used in 18 children. Only one child used a Hickman catheter.

The patients with primary intestinal failure were diagnosed with short bowel syndrome (36.8%), chronic intestinal pseudo-obstruction (26.3%), intractable diarrhea of infancy (26.3%), and other diagnoses (10.5%). Among the seven short bowel syndrome patients, four had neonatal-onset. One of the patients with other diagnoses had cerebral palsy with cyclic vomiting syndrome and severe feeding intolerance. The other patient had a feeding disorder and chronic diarrhea after liver transplantation due to biliary atresia.

#### Complications

Thirteen patients developed CRBSIs while receiving PN; the incidence was 2.7/1,000 catheter-days.

| Table 1. Patient Characteristics |
|----------------------------------|
| **Variable**                     | **Value**               |
| Age (yr)                         | 9.9 (1.3-21.6)         |
| Gender                           |                         |
| Male                             | 8 (42.1)               |
| Female                           | 11 (57.9)              |
| Age at PN initiation (yr)        | 1.3 (0.04-17.9)        |
| Duration of PN treatment (yr)    | 2.9 (0.67-13.0)        |
| Central catheter                 |                         |
| Chemoport                        | 18 (94.7)              |
| Hickman                          | 1 (5.3)                |
| Etiology                         |                         |
| Short bowel syndrome             | 7 (36.8)               |
| Chronic intestinal pseudo-obstruction | 5 (26.3)         |
| Intractable diarrhea of infancy  | 5 (26.3)               |
| Other diagnoses                  | 2 (10.5)               |

Values are presented as median (range) or number (%). PN: parenteral nutrition.
The patients who developed CRBSIs had younger ages at PN initiation and lower initial height Z-scores, as determined by the Mann-Whitney test ($p=0.014$, $p=0.011$). Patients’ underlying diagnoses were not significant risk factors.

Six patients developed catheter-related thrombosis; the incidence was 0.25/1,000 catheter-days (Table 2). Two of them had an initial symptom of difficulty in flushing the catheter but four patients were asymptomatic. There were no significant predisposing factors, including the age at PN initiation, the patients’ underlying diagnoses, or the patients’ durations of PN therapy.

Eleven patients (57.9%) developed PNALD (Table 2), and all but one patient recovered. Patients’ ages, diagnoses, CRBSIs, enteral feeding tolerances, and treatment durations were not significantly related to PNALD.

All patients developed micronutrient deficiencies while receiving PN. The lifetime micronutrient deficiency percentages are included in Fig. 1. Patients who had received PN for over 3 years had a higher incidence of vitamin B12 deficiency, as determined by Fisher’s exact test ($p=0.023$). Their vitamin B12 deficiency risk was 14-fold greater than that of patients who had received PN for less than 3 years, as determined by binary logistic regression ($p=0.019$; Exp (B) OR=14.0; 95% CI 1.5-127.2). Patients with vitamin B12 deficiency exhibited longer PN treatment durations and lower final body weight Z-scores ($p=0.007$, 0.011). Patients with zinc deficiency exhibited lower initial height Z-scores, as determined by the Mann-Whitney test ($p=0.016$). No other micronutrient deficiencies were significantly related to PN therapy.

Of the seven short bowel syndrome patients, 57.1% had CRBSIs, 28.6% had catheter-related thrombosis and 71.4% had PNALD, and these percentages were not significantly different from the overall study group. All patients had vitamin D and copper deficiency, but none of them had vitamin B12 or zinc deficiency. Most of the patients had surgery that preserved the ileocecal valve, and this preservation could explain the absence of vitamin B12 deficiency. Remaining small intestine lengths were also analyzed for the short bowel syndrome patients. The median length of the remaining small intestine was 30 cm (missing data, $n=1$). CRBSIs, catheter-related thrombosis, and PNALD were not significantly related to remaining small intestine lengths.

All of the incidences of PN complications, includ-
ing micronutrient deficiencies, had decreased from the first year to the last year of the study except for the vitamin D deficiencies. None of the vitamin B12 and zinc deficiencies occurred during the last year of PN. Only one selenium deficiency occurred during the last year of PN.

**Final outcomes**

The patients’ final clinical outcomes are provided in Table 2. Two patients (10.5%) were weaned from PN and are currently receiving enteral feeding; 14 (73.7%) received PN with enteral feeding; and 3 patients (15.8%) died. The causes of death were malnutrition secondary to poor compliance, septic shock, and respiratory arrest secondary to underlying neuromuscular disease.

Enteral nutrition (EN) was started whenever possible in all patients. The main cause of maintaining only PN was feeding intolerance with vomiting or diarrhea. The median age at EN initiation was 1.5 years; the median duration of EN was 2.9 years. Age at EN initiation and EN duration were not related to any of the PN complications, including micronutrient deficiencies, or clinical outcomes. Nine patients had intermittent EN and ten patients had sustained EN. PN complications and clinical outcomes were not significantly related in either group.

The final mean PN calorie percentage with respect to the total calorie intake was 56.7%. PN calorie percentage was not significantly related to the weaning from PN and micronutrient deficiencies. Six patients had PN calorie percentages greater than 70%. Their PN complications, including micronutrient deficiencies and clinical outcomes, were not significantly different from those of the other patients. Of the 14 patients currently receiving PN, 6 (42.9%) were receiving hospital-mixed formulations, and 8 (57.1%) were receiving commercial PN bags.

One of the patients who developed PNALD underwent multi-visceral transplant that included the liver and intestine.

The overall survival rates at 2 and 5 years were 93.3% and 84.0%, respectively, as determined by the Kaplan-Meier method. The cumulative survival curve is displayed in Fig. 2. There were no factors significantly related to survival, including the age at PN initiation, the patient’s underlying diagnosis, and the duration of PN treatment.

**Final anthropometric outcomes**

Both the median body weight and BMI Z-score improved following PN treatment, as determined by the Wilcoxon signed rank test \( p = 0.049, p = 0.003 \). The height Z-score did not decrease compared with the baseline value.

A final body weight Z-score \(-2\) was significantly associated with CRBSIs, as determined by Fisher’s exact test \( p = 0.044 \). The patients with PNALD exhibited lower final body weight Z-scores and lower final height Z-scores, as determined by the Mann-Whitney test \( p = 0.026, p = 0.026 \). Patients’ underlying diseases were not significantly associated with growth failure.

**DISCUSSION**

Patients with chronic intestinal failure who were hospitalized at Seoul National University Children’s Hospital experienced acceptable clinical outcomes following long-term PN treatment.

Most likely due to the assistance of a multi-
Table 3. Comparison of the Clinical Outcomes

| Outcome                              | Present study | Previous studies |
|--------------------------------------|---------------|------------------|
| Two-year survival rate (%)           | 93.3          | 93.3 [14]        |
| CRBSIs (/1,000 catheter-days)         | 2.7           | 3.7-11 [20,22]   |
| Catheter-related thrombosis (/1,000 catheter-days) | 0.2-0.25     | 0.25 [24-27]     |
| PNALD (%)                            | 57.9          | 60.8 [33]        |

CRBSIs: catheter-related bloodstream infections, PNALD: parenteral nutrition-associated liver disease.

disciplined nutritional support team, the 2-year survival rate over the past two decades has improved from 70.6% (1990-1994) to 93.3% (2005-2009), based on the results of previous study [14]. The 2-year survival rate in the current study was 93.3%, which was similar to the aforementioned results (Table 3), but there was no significant factor that appeared to affect patient survival, including the age at PN initiation, patients’ underlying diagnoses, and treatment duration.

Previous reports indicated that the mortality rate during the initial years of HPN therapy was high and was apparently related to patients’ underlying diagnoses. Nevertheless, the mortality rate in the previous study was related to the adverse effects of long-term PN therapy in patients receiving long-term HPN [15]. Each of the three patients in the present study who died had received PN for over a year; two died due to complications of PN treatment, and one died due to an underlying disease.

A recent review demonstrated that the risk factors for survival included prematurity, an age less than 2 years, an underlying diagnosis (necrotizing enterocolitis, congenital mucosal disease), the lack of a professional nutritional support team, and liver failure due to intestinal failure-associated liver disease. An ultra-short bowel and the existence of a stoma were each risk factors for short bowel syndrome in children. Other HPN-related complications were not related to the survival rate [16].

Previously, researchers hypothesized that patients with inflammatory bowel disease and short bowel syndrome had the best outcomes, as well as that patients with intractable diarrhea of infancy had the lowest survival rate. In one study, patients with chronic intestinal pseudo-obstruction were also found to have low survival rate [17]. However, the current study revealed no relationship between survival and patients’ diagnoses.

The overall incidence of CRBSIs was higher among patients who had received HPN for over 90 days compared with patients who had received HPN for less than 30 days [18]. Therefore, the references pertaining to patients receiving PN for over 30 days were reviewed. The documented incidence of CRBSIs in children was 0.9-11/1,000 catheter days [19-22]. The overall incidence increased to 3.7-11/1,000 catheter days if studies that did not utilize ethanol-lock therapy were reviewed [20,22]. The incidence of CRBSIs in the present study was 2.7/1,000 catheter-days, in the absence of ethanol-lock therapy (Table 3). Therefore, bloodstream infections were well-controlled compared with the previous study results. Based on the results of previous studies, patients with intestinal failure had the highest incidence of CRBSIs during the first month of HPN therapy. Additionally, the infants had a significantly higher incidence of bloodstream infections compared with older children, and an age of less than 3 years was a significant risk factor [18,22]. This finding was consistent with the results of this study, as the majority of patients who developed a bloodstream infection began receiving PN at a younger age.

It has been suggested that patients with short bowel syndrome develop more CRBSIs than patients with chronic intestinal pseudo-obstruction syndrome [23]. The present study demonstrated that patients’ underlying diagnoses were not significant risk factors for bloodstream infection.

The incidence of catheter-related thrombosis was thought to be higher in children, as they have smaller blood vessels than adults [24]. The incidences of catheter-related thrombosis were 33% and 0.2-0.25/1,000 catheter-days in previous reports (Table 3), the results of which were similar to the results of this study (31.6%, 0.25/1,000 catheter-days) [24-27]. No factor, including the age at PN initiation, patients’
underlying diagnoses, and the duration of PN treatment, appeared to significantly influence these results.

Several studies have suggested that the incidence of catheter-related thrombosis did not significantly correlate to the duration of central venous catheterization [28-32]. From a previous report, catheter-related thrombosis occurred mainly in the 8 days after catheterization and showed a similar prevalence during the study period. This occurrence was explained by the fact that the endothelial damage due to the vein puncture was healed in the 8 days after catheterization and the thrombosis developed mostly in the first days after catheterization. Therefore, the overall catheter-related thrombosis incidence was similar during the study period [28]. In the present study, all of the patients had more than six months of total central venous catheter duration, which would not have affected the catheter-related thrombosis incidence.

Based on previous mixed-population results, the incidence of PNALD was 49.8%. However, the incidence of PNALD in children receiving long-term PN treatment (>60 days) was 60.8% [33]. The incidence of PNALD was 57.9% in the present study, which was consistent with the results of previous studies in patients receiving long-term PN treatment (Table 3). Each of the patients with PNALD recovered, with the exception of one patient who underwent multi-visceral transplantation.

The risk factors for intestinal failure-associated liver disease included age, prematurity, diagnosis, CRBSIs, bacterial overgrowth, and enteral feeds. Treatment-associated risk factors included PN composition, PN duration, surgical procedure outcomes, and toxicity due to antibiotics [34]. Based on the results of the current study, factors such as age, underlying diagnoses, CRBSIs, enteral feeding tolerance, and PN duration were not related to the development of PNALD.

Micronutrient deficiency studies were undertaken only during the parenteral nutrition to enteral nutrition transition period, as well as following the initiation of full enteral feeding. As the patients in this study were receiving primarily PN by the end of the study, the aforementioned review included only the transition period. Based on the results of previous studies, multiple micronutrient deficiencies occurred most often during the transition period, and mineral deficiencies were more frequent than vitamin deficiencies. Therefore, the authors recommended that manufacturers produce mineral supplements for patients receiving long-term PN. A significantly higher incidence of mineral deficiencies was noted among the children with weight-for-age Z-scores < −2 and height-for-age Z-scores < −2 during the transition period [13]. Another study revealed that the incidence of mineral deficiency was significantly lower among patients with higher height-for-age Z-scores [35]. These results were consistent with those of the current study, as we determined that patients with zinc deficiency had lower initial height-for-age Z-scores.

In this study, the risk of vitamin B12 deficiency was greater among the patients who had received PN for more than 3 years compared with the patients who had received PN for less than 3 years. This result may be explained by the fact that the initial multivitamin formulation, M.V.H.® (Whanin Pharm. Co., Ltd., Seoul, Korea), did not contain vitamin B12. The introduction of an intramuscular vitamin B12 injection and Tamipool® (Celltrion, Inc., Incheon, Korea), which consisted of a multivitamin including vitamin B12, might have corrected this deficiency.

Vitamin B12 and zinc deficiencies were common in this study group. However, 78% of the vitamin B12 deficiencies occurred in the first year of PN and were corrected with the sustained supply. In addition, none of the vitamin B12 and zinc deficiencies occurred during the last year of PN. These results may be supported by the improvement of the PN composition with micronutrients over the study period, such as changing the multivitamin formulation M.V.H.® to vitamin B12 consisting Tamipool® or administering an intramuscular vitamin B12 injection. All of the zinc deficiencies were transient and were corrected after changing the PN composition according to the regular monitoring. Furthermore, the low-
est zinc levels were all greater than 65 μg/dL.

The results of a previous study indicated that folate deficiency was not detected during the transition period, most likely as a result of intraluminal bacterial folate production [13,36]. However, folate deficiency was common among the patients in this study group (89.5%).

Comparing the first year to the last year of the study, all of the incidences of PN complications, including micronutrient deficiencies, had decreased except for the vitamin D deficiencies. This decrease could be explained by the fact that vitamin D may be supplied more effectively per oral than an intravenous route, but the patients had difficulty taking oral supplements due to their symptoms and had decreased bowel absorption due to their underlying disease. Only one event of CRBSI and PNALD occurred during the last year of the study. During the last year of PN, vitamin B12 and zinc deficiencies were not present, and only one selenium deficiency was detected. This occurrence could be explained by the improvement of PN composition with micronutrients and PN management over the study period.

In the present study, children receiving long-term PN treatment experienced improvements in their body weights and BMI, and their heights did not decrease compared with their baseline values. The reasons for their short stature were not significantly associated with growth failure in this study.

The present study was involved rare nutritional outcomes, including micronutrient deficiencies, and anthropometric measurements associated with long-term PN.

There were several limitations of the present study, due to both its small sample size and its retrospective design. Because the incidence of chronic intestinal failure with the treatment of HPN over 6 months is rare in the pediatric population and because it is difficult to predict the patient outcomes, a prospective study could not be designed easily. The study was conducted at a single center in a homogeneous ethnic group, and the results may be different if a study was conducted in a multicenter heterogeneous group. However, the data from this center may be regarded as the general outcome of chronic intestinal failure in children in Korea because this center is the largest children’s hospital in the country.

PN is both a crucial and a relatively safe treatment for patients with pediatric intestinal failure. CRBSIs and PNALD were significantly related to the final anthropometric measurements. Although most of the PNALD events were transient and improved shortly after supportive management, PNALD influenced the nutritional outcomes.

Transient micronutrient deficiencies, which were generally corrected after changing the PN composition, were frequently observed among these patients. Body weight, height and BMI Z-scores did not decrease compared with initial values.

Controlling PN complications and closely monitoring patients’ individual anthropometric measurements and micronutrient levels are necessary for successful PN therapy.

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