Effects of cyclic parenteral nutrition on parenteral nutrition-associated cholestasis in newborns

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ABSTRACT

Background and Objectives: Parenteral nutrition (PN) is one of the main nutritional methods used in newborns; however, long-term PN may induce PN-associated cholestasis (PNAC). This study aims to evaluate the effect of cyclic PN in the prevention and improvement of PNAC in newborns requiring long-term PN. **Methods and Study Design:** A retrospective cohort study was conducted on patients admitted at the Seoul National University Children's Hospital neonatal intensive care unit between October 2010 and September 2015 and referred to the nutrition support team with total parenteral nutrition for more than 14 days. The primary outcome was the incidence of PNAC. The incidence of hypoglycemia, changes in direct bilirubin (DB) concentrations, and length of hospital stay were investigated. **Results:** A total of 124 patients were observed in this study. Among these, 100 patients received continuous PN, whereas 24 patients received both continuous and cyclic PN. PNAC occurred in 31.5% (39/124) of study population. The incidence rates of PNAC were 27.4% during continuous PN period and 20.8% during cyclic PN period. Cyclic PN was an independent factor that significantly decreased PNAC incidence (OR=0.154; 95% CI, 0.045-0.529, p=0.003). DB concentrations significantly decreased (p=0.049) with therapeutic cyclic PN, but remained normal with prophylactic cyclic PN. No significant difference in hypoglycemia incidence and length of hospital stay was observed in both continuous PN and continuous to cyclic PN groups. **Conclusions:** Cyclic PN could be effective in the prevention and improvement of PNAC and also safe in terms of hypoglycemia in newborns.

Key Words: infant, newborn, intensive care units, neonatal, cholestasis, parenteral nutrition, cyclic

INTRODUCTION

Parenteral nutrition (PN) is the main nutritional method used in premature infants or infants suffering from gastrointestinal diseases. However, long-term PN may induce PN-associated cholestasis (PNAC); PNAC and intestinal failure-associated liver disease was reported in 29.9% of all pediatric patients and in 49.8% of those with intestinal failure.[1-2] Prematurity, necrotizing enterocolitis (NEC), PN duration, sepsis, lack of enteral nutrition, and PN deficiency or toxicity have been suggested as risk factors for PNAC. On the other hand, trophic feeding, cyclic PN, taurine, fish oil-based lipid emulsion, ursodeoxycholic acid (UDCA), and erythromycin are known to be effective in the prevention of PNAC.[3-10]

Cyclic PN is the intermittent administration of intravenous fluids with regular infusion breaks.[11] It is administered as a single 10- to 14-hour infusion, but may range from 8 to 23 hours.[12] Although a systemic review reported that prophylactic cyclic PN reduces PNAC incidence,[4] cyclic PN cannot be started without some degree of enteral supplementation in premature infants with insufficient glycogen reserves. Little is known about the effects of cyclic PN in premature infants. Also, there are no standardized clinical practice guidelines on cyclic PN administration in the neonatal intensive care unit (NICU).

The Seoul National University Children's Hospital (SNUCH) nutrition support team (NST) has been providing nutrition support for newborns in the NICU; particularly, it has been utilizing cyclic PN for PNAC treatment and prevention since 2010. Therapeutic cyclic PN is given when PNAC occurs, and if long-term PN is needed, cyclic PN is given to prevent PNAC. Previous studies on pediatric cyclic PN have applied a 6- to 12-hour off-time.[13-15] However, a 1- to 2-hour off-time is used to reduce the risk of hypoglycemia in newborns.

This study aims to evaluate the effects of cyclic PN with short off-time in the prevention and improvement of PNAC in newborns on long-term PN. Also, the clinical outcomes in both continuous PN and continuous to cyclic PN groups were compared.

MATERIALS AND METHODS

Study population

Newborns (gestational age (GA) 23-40 weeks, birth weight ≤4.0 kg) admitted in the NICU at SNUCH between October 2010 and September 2015 and referred to the NST with subsequent total parenteral nutrition (TPN) for 14 days or more were enrolled in the study. Those who were born in other hospitals, transferred to another hospital, or died before discharge were excluded from the study. Infants whose direct bilirubin (DB) concentrations were not measured during the PN period and those with cholestasis before PN initiation were also excluded from the study.

This study was approved by the institutional review board of the SNUCH (IRB No. H-1511-111-723). The study conforms to the provision of the Declaration of Helsinki in 1995 (as revised in Fortaleza 2013).

Data extraction and study methods

A retrospective cohort study was conducted and data was collected through electronic medical records. The patients' baseline characteristics were collected as follows: GA, sex, birth weight, small for gestational age (SGA), multiple births, type of delivery, Apgar score at 1 min and 5

min, common newborn problems and diseases (respiratory distress syndrome, broncho-pulmonary dysplasia (BPD), patent ductus arteriosus (PDA), NEC, culture proven sepsis), underlying diseases (congenital disorders, liver diseases, metabolic diseases), and medications (UDCA, erythromycin). PDA was defined as the need for treatment such as medication or surgery, NEC as Bell's criteria stage II or higher,[16] and culture-proven sepsis as the case of bacterial identification in blood cultures.

Maternal age, medical history, type of membrane rupture, and perinatal medications were investigated. Collected data regarding nutritional therapy included PN period and duration of PN administration, method of nutritional support and nutrient supplies, type of amino acid solution and intravenous fat emulsion (IVFE), and method of cyclic PN.

Newborns requiring PN received mostly 2 in 1 customized TPN. Pediatric amino acid solutions such as Primene (Baxter) and Trophamine (JW Pharmaceutical) were given. The IVFE provided was either medium-chain triglyceride/long-chain triglyceride (MCT/LCT) (Dongkook Pharmaceutical) or SMOFlipid (Fresenius Kabi). Amino acid is usually started at a dose of 1.5-2.0 g/kg/day and is increased daily (increments of 0.5-1 g/kg/day) to a goal dose of 3-4 g/kg/day for newborns. IVFE is usually started at a dose of 0.5-1 g/kg/day and is increased daily (increments of 0.5-1 g/kg/day) to a goal dose of 3–4 g/kg/day for newborns.

Cyclic PN was defined as PN with a scheduled duration of <24 hours per day.[15] After the initial administration of continuous PN, cyclic PN was given when PNAC occurred or given as a prophylaxis in newborns requiring long-term PN. The continuous to cyclic PN group was defined as the group that switched from continuous PN to cyclic PN with a 1- to 2-hour off-time. Saline or Hartmann solution was infused during off-time. When serum glucose concentration showed a tendency to decrease, it used to be substituted by a low concentration (usually 5 to 10%) dextrose solution temporarily or continuously. Both 2 in 1 customized TPN and IVFE were discontinued during off-time. The infusion rate of TPN was gradually reduced before off-time and increased after off-time every 1 to 2 hours. The administration sets for PN solution were changed with each new PN container. At the beginning of cyclic PN administration after off-time, the PN container and administration sets were replaced daily.

The incidence of PNAC during PN period was the primary outcome. The presence of intestinal failure with PNAC was investigated. The classification of the intestinal failure was based on the European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations.[17] The method of PN administration at the time of PNAC occurrence was observed in the continuous to cyclic PN group. Changes in DB concentrations were compared between patients treated with therapeutic cyclic PN at DB ≥2 mg/dL and those who

maintained continuous PN ≥3 days after PNAC occurrence (the first DB ≥2 mg/dL). The changes in DB concentrations before and after cyclic PN were evaluated in patients who received prophylactic cyclic PN. The incidence of hypoglycemia, length of NICU stay, and length of total hospital stay (secondary outcomes) were compared between the continuous PN group and the continuous to cyclic PN group. PNAC was defined as DB 2.0 mg/dL or greater,[7] and hypoglycemia as serum glucose concentration less than 40 mg/dL.[18]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 22.0. Continuous variables were analyzed by t-test or Mann-Whitney test, and categorical variables by chi-square test or Fisher's exact test. Binary logistic regression was performed to confirm the effects of cyclic PN on PNAC. *p* values less than 0.05 were considered statistically significant.

RESULTS

A total of 891 patients were admitted in the SNUCH NICU and referred to the NST from October 2010 to September 2015. Among these, a total of 306 patients were excluded due to the following reasons: born in another hospitals, transferred to another hospital, or died before discharge. Additionally, 423 patients with PN of less than 14 days, 34 patients without DB concentrations during the PN period, and 4 patients with cholestasis before PN initiation were also excluded. As a result, a total of 124 patients were included in this study.

Among the 124 patients, 24 (19.4%) received continuous PN and cyclic PN, whereas 100 (80.6%) only received continuous PN. The patients' baseline characteristics are shown in Table 1. GA, birth weight, BPD, PDA treatment, culture-proven sepsis, PN duration, and UDCA were significantly different between the two groups. The continuous PN group exhibited lower GA and birth weight, along with higher incidence of BPD and percentage of treated PDA. On the contrary, the incidence of sepsis, the duration of PN administration, and the rate of UDCA administration was significantly higher in the continuous to cyclic PN group.

Table 2 shows the nutritional intake on day 7 and day 14 after starting PN administration in both groups. In both groups, enteral nutrition (EN) calories were significantly increased at day 14 than on day 7, and PN calories were significantly decreased. The nutritional intake between the two groups on day 7 and day 14 were not significantly different.

The median value of total PN duration was 59.5 days (IQR 47.5-69 days) while that of cyclic PN duration was 26.5 days (IQR 14.5-37 days) in the continuous to cyclic PN group

(N=24). At the time of transition to cyclic PN, mean postmenstrual age was 37.2±4.68 weeks, mean postnatal days was 42.3±24.1 days, and mean body weight was 2.01±0.65 kg. At the 35th day (IQR 24.5-51 days) after PN initiation, continuous PN was changed to cyclic PN.

Six patients (25.0%) received prophylactic cyclic PN before the occurrence of PNAC, whereas 13 patients (54.2%) were treated with cyclic PN after PNAC occurrence. Five patients had unmeasured DB concentrations before the administration of cyclic PN.

The cyclic PN off-time was 1 to 2 hours (70.8% 1 hour; 29.2% 2 hours), and saline or Hartmann solution was infused during off-time. The off-time solution was switched to low concentration (5-10%) dextrose solution in 9 patients (37.5%) due to the decrease in serum glucose concentrations. However, all exhibited glucose concentration > 40 mg/dL except for one case.

Among the 124 patients observed, 39 (31.5%) patients developed cholestasis during the PN period. Within this group of patients, 21 were in the continuous PN group and 18 were in the continuous to cyclic PN group (Figure 1). The continuous to cyclic PN group also went through continuous PN period before switching to cyclic PN. Therefore, incidence of PNAC occurrence during continuous PN was obtained from both continuous PN group and continuous to cyclic PN group. PNAC during continuous PN administration occurred in 34 (Con 21, ConCy_Con 13) of 124 patients (Con 100, ConCy_Con 24) who received continuous PN (27.4%). Among 24 patients who received cyclic PN, 5 patients developed PNAC during cyclic PN period (20.8%).

Most of the patients with PNAC (31/39, 79.5%) had intestinal failure. There were 28 cases of gastrointestinal surgery due to NEC, omphalocele, intestinal atresia and others. There were 2 cases of obstruction, and 1 case of intestinal dysmotility caused by viral gastroenteritis. Five of the eight patients without intestinal failure were extremely low birth weight infants who were highly dependent upon parenteral nutrition (PN). One patient developed cholestasis due to sepsis, another patient developed cholestasis due to prolonged NPO status before and after open heart surgery, and the other patient developed cholestasis due to long-term PN with hypoxic ischemic encephalopathy.

Logistic regression analysis showed that the transition from continuous to cyclic PN decreased the risk of PNAC after adjusting for GA, sex, birth weight, duration of PN, sepsis, BPD, and PDA treatment (OR=0.154; 95% CI, 0.045-0.529, p=0.003) (Table 3).

Changes in DB concentrations were compared between 13 patients who were treated with therapeutic cyclic PN at DB ≥2 mg/dL and 16 patients who maintained continuous PN more than 3 days after PNAC occurrence (the first DB ≥2 mg/dL). DB concentration decreased

from 4.37±1.86 mg/dL before cyclic PN administration to 3.58±2.05 mg/dL for 14 days after cyclic PN initiation (p=0.049). In the group that maintained continuous PN after PNAC occurrence, DB concentrations decreased from 2.53±0.48 mg/dL to 2.12±1.00 mg/ dL (p=0.047) (Figure 2).

In six patients who received prophylactic cyclic PN, DB concentrations remained normal for the administration period; the mean DB concentration was 1.04±0.58 mg/dL before cyclic PN initiation and 0.83±0.66 mg/dL after 14 days of cyclic PN (p=0.259).

Hypoglycemia occurred in 16.1% (20/124) of the total patients during hospitalization. The incidence of hypoglycemia in the continuous PN group was 16.0% (16/100), and the incidence of hypoglycemia in the continuous to cyclic PN group was 16.7% (4/24). Nine (9/124, 7.3%) experienced hypoglycemia during the PN period (Con 7, ConCy 2) and 11 patients (11/124, 8.9%; 8 occurred on the birth day) experienced before or after the PN period (Con 9, ConCy 2). As in the case of PNAC occurrence, incidence of hypoglycemia occurrence during continuous PN was obtained from both continuous PN group and continuous to cyclic PN group. Hypoglycemia occurred in 8 (Con 7, ConCy_Con 1) of 124 patients (Con 100, ConCy_Con 24) during continuous PN period (6.5%). Among 24 patients who received cyclic PN, 1 patient occurred hypoglycemia during cyclic PN period (4.2%) (p=1.000).

Despite the longer PN duration in the continuous to cyclic PN group, length of NICU stay (median (IQR); continuous PN 87 days (65.5-110.5 days) vs. continuous to cyclic PN 92 days (65.5-138.5 days), p=0.753) and total hospital stay (median (IQR); continuous PN 89 days (68-111.75 days) vs. continuous to cyclic PN 99 days (65.5-148.25 days), p=0.820) showed no difference between the two groups.

DISCUSSION

In our study, PNAC occurred in 31.5% (39/124) of the study population and 87.2% (34/39) in the continuous PN period. Logistic regression analysis revealed that cyclic PN was an independent factor in reducing the risk of PNAC. DB concentrations were significantly decreased in patients who suffered from severe direct hyperbilirubinemia (DB concentrations ≥4.0 mg/dL on average) and received cyclic PN therapeutically. Despite the small number of patients (6/24, 25.0%), DB concentrations remained normal after the administration of prophylactic cyclic PN. These results suggest that cyclic PN could be effective in the prevention and improvement of PNAC in newborns that require long-term PN. It was suggested that cyclic PN mimicked the physiological pattern of oral feeding by increasing

lipid oxidation and by decreasing carbohydrate oxidation during the fasting phase of the cyclic regimen. Meanwhile, during continuous PN, mainly carbohydrate was utilized throughout the day and consequently oxidized no lipids.[19] These differences in substrate utilization suggest that cyclic PN may reduce the risk of PNAC.

The effect of cyclic PN on PNAC was shown to be favorable in many other studies. Collier et al[13] reported that DB concentrations decreased or stabilized after the administration of cyclic PN in infants <6 months of age. Jensen et al[14] reported that the cumulative incidence of hyperbilirubinemia decreased when prophylactic cyclic PN was given in neonates with gastroschisis. In this study, surgical neonates were included, whereas infants with extremely low birth weights were excluded. The mean birth weight and GA for the study population of the aforementioned study were 2.54 kg and 36 weeks, respectively; these were higher compared to those of our study, which were 1.26 kg and 29.3 weeks, respectively.

On the other hand, in a RCT on early cyclic PN for cholestasis prevention in very low birth weight infants (VLBWI), the incidence of PNAC was reported to be similar in both cyclic PN and continuous PN groups.[20] In this study, infants of the cyclic PN group received amino acid solutions for over 20 hours and IVFE for over 18 hours, but dextrose was given for over 24 hours without off-time. Thus, the results of this study may not be adequate to demonstrate the effect of cyclic PN.

Confounding factors such as enteral feeding and parenteral nutrients should be considered when evaluating the effects of cyclic PN on PNAC. Jensen et al[14] reported that enteral feeding (mean percentage of goal, 110 kcal/kg per day) affected the development of PNAC (HR 0.94; 95% CI, 0.89-1.00, p=0.042). Salvador et al[20] suggested that the postnatal day of full enteral nutrition (OR 1.38; 95% CI, 1.02-1.88, p=0.04) may be an independent risk factor for the development of cholestasis. Gupta et al[21] proposed that daily intravenous dextrose was associated with PNAC in premature infants (OR 1.7; 95% CI, 1.04-2.9, p=0.03). In our study, there is no difference in the supply of macronutrients between the continuous PN and continuous to cyclic PN groups, including EN calories, PN calories, and dextrose of day 7 and day 14. Several studies reported that fatty emulsions containing fish oil (FO) could prevent PNAC.[22-26] The subjects received a mixture of MCT/LCT or FO-based IVFE, SMOFlipid. The ratio of SMOF lipid between the two groups had no significant difference.

A large number of VLBWIs were included in the continuous to cyclic PN group (45.8%, 11/24); for these patients, initial continuous PN was maintained until they reached 37.2 weeks of average post menstrual age (PMA), at which they converted to cyclic PN. Cyclic PN was given after PNAC occurrence (54.2%, 13/24). Nghiem-Rao et al[15] compared the effects of

prophylactic cyclic PN and therapeutic cyclic PN in surgical neonates. The prophylactic cyclic PN group showed a low incidence of hyperbilirubinemia and low conjugated bilirubin at the maximum concentration. This result suggests that early prophylactic cyclic PN initiation helps surgical neonates with gastrointestinal problems requiring long-term PN. Infants weighing ≥2 kg with a median birth weight of 2.54 kg and a median GA of 34 weeks were candidates for cyclic PN. Infants with hypoglycemia during cyclic PN administration had a lower median weight and PMA; therefore, further research regarding cyclic PN administration in different levels of newborn maturity is necessary.

In children younger than 2 years of age, abrupt discontinuation of PN infusion causes hypoglycemia.[27] Previous studies have shown that hypoglycemia of 20% was observed within 120 minutes even if PN was discontinued as a tapering regimen in children younger than 3 years of age. (up to 55% if abruptly discontinued).[28] Especially, preterm infants are vulnerable to hypoglycemia because of low glycogen storage and low enzyme activity.[29] Liver carbohydrate storage is low until 36 week gestation, and is rapidly depleted within 6 hours of delivery even in the case of term infants.[30] Unlike previous studies on neonatal cyclic PN, a large number of VLBWIs vulnerable to hypoglycemia were included in our study, therefore cyclic PN with short off-time was applied due to risk of hypoglycemia. In our study, hypoglycemia in the continuous to cyclic PN group was similar to those of the continuous PN group. This result is due to the following reasons: the scheduled off-time was shortened to 1 to 2 hours in the cyclic PN period, low concentration dextrose solution was maintained as needed, and a gradual tapering off regimen was used.

Standardized clinical guidelines on cyclic PN administration in premature infants are not currently available. Our study showed that cyclic PN should be used to prevent PNAC in newborns that require more than 14 days of long-term PN and to improve PNAC in newborns. Cyclic PN with short off-time are given in neonates including VLBWI without increasing the risk of hypoglycemia. As needed, a low concentration dextrose solution is administered to prevent severe hypoglycemia during off-time.

This study has limitations of a retrospective study design conducted in a single center. Thus, a large-scale RCT is needed to compare the effects of continuous PN, prophylactic cyclic PN, and therapeutic cyclic PN.

The results of our study show that cyclic PN with a 1- to 2-hour off-time is effective in the prevention and improvement of PNAC and is also safe even in terms of hypoglycemia in newborns.

AUTHOR DISCLOSURE

The authors declare that they have no conflict of interest.

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Table 1. Baseline characteristics

	Total (N=124)	Continuous PN (N=100)	Continuous to cyclic PN (N=24)	*p* value
GA (weeks), mean±SD	29.29±4.84	28.84±4.63	31.14±5.34	0.037*
Sex, men, n (%)	71 (57.3)	57 (57.0)	14 (58.3)	0.906
Birth weight (kg), mean±SD	1.26±0.84	1.18±0.81	1.57±0.89	0.042*
Birth weight Z score, mean±SD	-0.45±1.10	-0.42±1.06	-0.56±1.28	0.581
SGA, n (%)	33 (26.6)	26 (26.0)	7 (29.2)	0.753
Multiple, n (%)	57 (46.0)	46 (46.0)	11 (45.8)	0.988
Cesarean delivery, n (%)	70 (56.5)	54 (54.0)	16 (66.7)	0.261
Apgar score 1 min, mean±SD	3.82±2.16	3.77±2.13	4.04±2.33	0.582
Apgar score 5 min, mean±SD	6.05±1.80	6.04±1.75	6.08±2.04	0.916
RDS, n (%)	72 (58.1)	59 (59.0)	13 (54.2)	0.667
BPD, n (%)	84 (67.7)	74 (74.0)	10 (41.7)	0.002*
PDA, treatment, n (%)	79 (63.7)	69 (69.0)	10 (41.7)	0.012*
NEC, n (%)	28 (22.6)	20 (20.0)	8 (33.3)	0.161
Culture proven sepsis, n (%)	51 (41.1)	35 (35.0)	16 (66.7)	0.005*†
PN duration (days), median (IQR)	28.5 (20.00-51.25)	24.00 (19.00-34.75)	59.50 (47.50-69.00)	<0.001*
SMOFlipid, n/N (%)	86/118 (72.9)	69/94 (73.4)	17/24 (70.8)	0.800
UDCA, n (%)	40 (32.3)	21 (21.0)	19 (79.2)	<0.001*
Erythromycin, n (%)	46 (37.1)	34/100 (34.0)	12 (50.0)	0.145

PN: parenteral nutrition; GA: gestational age; SGA: small for gestational age; RDS: respiratory distress syndrome; BPD: broncho-pulmonary dysplasia; PDA: patent ductus arteriosus; NEC: necrotizing entero-colitis; UDCA: urso-deoxy-cholic acid.
†Mann-Whitney test
*p <0.05.

Table 2. Nutritional intake

	Continuous PN (N=100)`			Continuous to cyclic PN (N=24)		
	Day 7	Day 14	*p* value	Day 7	Day 14	*p* value
EN, calorie (kcal/kg)	12.08±17.95	28.93±33.39	<0.001*	9.53±16.41	25.01±35.36	<0.001*
PN, calorie (kcal/kg)	74.03±21.51	67.27±29.74	0.026*	79.08±25.63	66.58±36.55	0.013*
PN, amino acid (g/kg)	2.94±0.79	2.57±1.09	0.001*	2.98±0.57	2.30±1.23	0.068
PN, lipid (g/kg)	2.17±1.02	1.78±1.28	0.007*	2.27±1.10	1.68±1.28	0.598
PN, GIR (mg/kg/min)	7.37±2.58	7.11±3.17	0.392	8.06±2.99	7.34±3.89	0.003*

PN: parenteral nutrition; EN: enteral nutrition; GIR: glucose infusion rate.
*p <0.05

Table 3. PNAC incidence (logistic regression)

Covariate	OR	95% CI	*p* value
Continuous to cyclic PN	0.154	0.045-0.529	0.003*
Culture proven sepsis	0.490	0.181-1.327	0.161
GA, <28 weeks	2.686	0.614-11.756	0.190
PN duration (days)	1.009	0.992-1.027	0.291
Sex, men	0.623	0.244-1.592	0.322
Birth weight, <1 kg	0.449	0.092-2.197	0.323
PDA, treatment	0.572	0.152-2.158	0.410
BPD	1.944	0.338-11.200	0.457

PNAC: PN-associated cholestasis; OR: odds ratio; CI: confidence interval; PN: parenteral nutrition; GA: gestational age; PDA: patent ductus arteriosus; BPD: broncho-pulmonary dysplasia.
*p <0.05

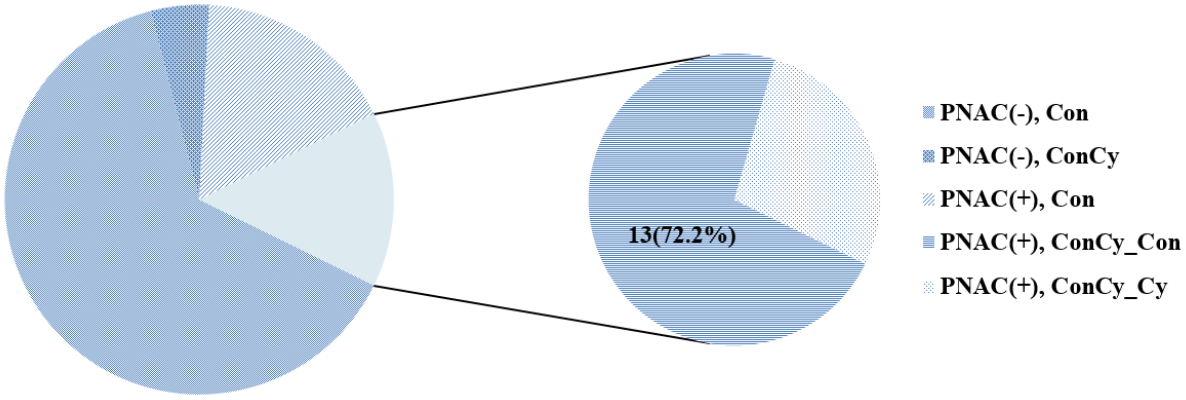

Figure 1. PNAC incidence. PNAC: PN-associated cholestasis; Con: continuous PN; ConCy: continuous to cyclic PN; ConCy_Con: continuous PN period of continuous to cyclic PN; ConCy_Cy: cyclic PN period of continuous to cyclic PN.

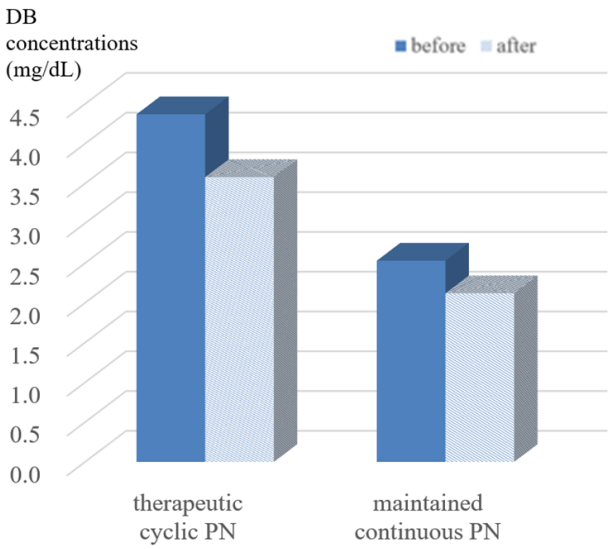

Figure 2. Changes in direct bilirubin concentrations. DB: direct bilirubin; PN: parenteral nutrition. *p <0.05.