Composition of parenteral nutrition solution affects the time of occurrence but not the incidence of cholestasis in surgical infants

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Parenteral nutrition-associated cholestasis (PNAC) is one of the most important complications of parenteral nutrition (PN). This study was conducted to define the incidence, characteristics and precipitating factors of PNAC in infants treated with two different PN regimens in the pediatric surgery department.

The records of infants who received two different PN regimens during January 2000-May 2008 (Group 1) and June 2008-May 2012 (Group 2) were reviewed retrospectively. Patients with and without PNAC comprised the study (Groups 1a-2a) and control groups (Groups 1b-2b), respectively.

With Group 1 (n=109) and Group 2 (n=46) constituted as indicated, Group 1a (n=13), Group 1b (n=32), Group 2a (n=6) and Group 2b (n=8) were evaluated. The incidence of PNAC was 14.1% (n=22), and the type of PN regimen did not affect the incidence (14.6% vs. 13.0%, p=0.39). The duration of PN was longer in Group 1a than in Group 1b (34±37 vs. 13±10 days, p=0.01), and longer in Group 2a than in Group 1a or Group 2b (146±148 vs. 34±37 days, p=0.02, and 14.0±5.9 days, p=0.002). PNAC developed later in Group 2a than in Group 1a (42.0±24.6 vs. 9.0±8.3 day, p=0.02). The lipid dosage was higher in Group 1a than in Group 1b (3.5±0.7 vs. 3.45±0.54 g/kg/day, p=0.001) or Group2a (2.2±0.4 g/kg/day, p=0.01). The lipid dosage was also higher in Group 2a than in Group 2b (p=0.001).

Two different regimens resulted in similar PNAC rates. The composition of nutrients in PN solution affects the time of occurrence but not the duration of PNAC. PNAC should be detected as early as possible and treated promptly.

Key words: cholestasis, infant, parenteral nutrition, surgery, hyperbilirubinemia, neonate.

Parenteral nutrition (PN) may cause hepatobiliary system complications such as fatty liver, bile duct and gall bladder injuries and cholestasis[1]. Cholestasis is an important complication of PN; it is defined as increased conjugated bilirubin levels (above 2.0 mg/dl) during PN treatment[2,3]. Serum gamma-glutamil transferase (GGT), alanine amino transferase (ALT), serum aspartate amino transferase (AST) and alkaline phosphatase levels usually increase as well.

PN-associated cholestasis (PNAC) is encountered in 14-60% of newborns who receive PN treatment[4-7]. The pathophysiology of PNAC is still obscure; its treatment is based on mainly enteral feeding, a cyclic PN regimen, binding bile acids with ursodeoxycholic acid, phenobarbital, erythromycin, a decrease in lipid concentration and the use of omega-3-containing lipid emulsion and control of sepsis[8-14]. There are also more recent data supporting the use of lipid restriction to treat PN-associated liver disease[15,16]. The present study was conducted to investigate

the relationship of lipid concentration and PNAC by looking at PN regimens containing two different lipid concentrations.

The study was conducted to define the incidence, characteristics and precipitating factors of PNAC in infants treated in the pediatric surgery department with two PN regimens containing different lipid concentrations.

Material and Methods

Data collection: The records of infants who received PN in the Neonatal Surgery Unit of the Pediatric Surgery Department from January 2000 to May 2012 (inclusive) were reviewed retrospectively. Patients with primary liver and/or biliary tree pathology were excluded. A serum conjugated bilirubin level over 2.0 mg/dL was defined as PNAC. The patients receiving PN that was prepared using a previous (January 2000-May 2008) and a new (June 2008-May 2012) method constituted Group 1 (n=109) and Group 2 (n=46), respectively. Within those groups, patients who developed PNAC were categorized as Group 1a and Group 2a, respectively. Patients who did not develop PNAC were the controls. The control groups (Group 1b and Group 2b) were constituted by randomly selecting patients from among the corresponding control patients. Primary surgical pathology, gender, body weight, gestational age, age at the beginning of PN, time elapsed until the diagnosis of cholestasis, duration of PNAC, duration of cholestasis, therapy for cholestasis, method of preparing the PN solution, lipid, protein and glucose concentrations and caloric content of the solution, sepsis status, presence of a central venous catheter and outcome were noted. The premature and low gestational age newborns in the study had been treated in another neonatal intensive care unit (ICU) in our institute.

The study was approved by the institutional ethics committee (431.10-2779).

Method of preparation and composition of PN solutions: PN solutions were ordered by pediatric surgeons and prepared by neonatal ward nurses up until May 2008 (Group 1). The Institutional Parenteral Solution Preparation Unit assumed responsibility after that date, with PN solutions prepared automatically and monitored by the Department of Pediatrics (Group 2). Group 1. Total volume of PN was calculated as 120% of the daily fluid requirement. Sodium chloride (50 ml, 3%), calcium gluconate (10 mEq), magnesium sulphate (6 mEq), N(2)-L-alanile L-glutamine (Dipeptiven®), heparin (500 IU, Liquemine®, Nevparin®), potassium (1-3 mEq/kg/day) and trace element solution (0.5 ml/kg/day Tracutil®) were included per 500 ml of PN solution. The initial lipid dose (10% or 20% Lipofundin®) was 1 g/kg and increased to 2 g/kg/day, 3 g/kg/day and 4 g/kg/day thereafter. The remaining PN fluid volume was replaced with equal volumes of carbohydrate (20% Dextrose®) and 6% or 10% amino acid (Trophamine® or Primene® respectively) solutions. Vitamins B, C and K were given daily. The electrolyte concentrations of the solutions were adjusted according to the results of periodic checks of serum electrolytes.

Group 2. Total volume of PN was calculated as 120% of the daily fluid requirement. Sodium (1-3 mEq/kg/day), calcium (1-3 mEq/kg/day), phosphorus (1.3 mmol/kg/day), potassium (1-3 mEq/kg/day), magnesium and trace elements (Tracutil®) and a vitamin mixture (Cernevit®) were added to PN solutions. The initial lipid dose (10% or 20% Lipofundin®) was 0.5-1 g/kg/day and gradually increased to a maximum dosage of 3 g/kg/day. The maximum dosage of amino acid solution (Primene® or Trophamine®) was 2.5-3.5 g/kg/day. Dextrose concentrations were 25 g/dl and 12.5 g/dl respectively in patients with and without a central venous line. The electrolyte concentrations of the solutions were adjusted according to the results of periodic checks of serum electrolytes.Complete blood count, peripheral smear and blood biochemistry were checked weekly and, urine glucose was checked daily using urosticks. Fresh frozen plasma (20 ml/kg) was transfused once a week.

The treatment regimen for PNAC consisted of enteral nutrition if possible, ursodeoxycholic acid (UDA), phenobarbital, cyclic parenteral nutrition, a decrease in lipid concentration and a change of the amino acid solution to one containing an increased amount of branched-chain amino acids and decreased amounts of methionine and aromatic amino acids (Hepatamine®).

Statistical analysis: Statistical analysis was performed using SPSS 16.0 software. The data were expressed as mean ± standard deviation

and range. The Mann-Whitney U and chi-square tests were used for analysis; p values lower than 0.05 were considered to be significant.

Results

One hundred fifty-five patients received PN during the study period. The numbers of patients receiving the previous and the new PN preparations were 109 and 46, respectively. PNAC was encountered in 22 (14.1%) patients; 16 (14.6%) of them had received the previous and 6 (13.0%) the new PN regimen. The type of PN regimen did not affect the rate of PNAC (p=0.39).

The primary pathologies were tracheoesophageal anomaly (n=26, 17%), intestinal atresia (n=18, 12%), gastroschisis (n=18, 12%), Hirschsprung's disease (n=15, 9%), necrotizing enterocolitis (n=8, 5%), duodenal obstruction (n=8, 5%), omphalocele (n=6, 4%) and Bochdalek hernia (n=5, 3%), along with others (n=51, 33%).

The patients whose detailed data were available made up Group 1a (n=13), Group 1b (n=32), Group 2a (n=6) and Group 2b (n=8). Demographic and clinical data of the groups are given in Table I.

Gestational age did not differ between Group 1a (36.0 ± 1.8 weeks, range: 32-39) and Group 2a (35.0 ± 2.2 weeks, range: 32-38) (p=0.24), or between Group 2a (35.0 ± 2.2 weeks, range: 32-38) and Group 2b (36.0 ± 2.3 weeks, range: 33-40) (p=0.94); however, it was lower in Group 1b (36.0 ± 2.5, range: 29-40) than in Group 1a (36.0 ± 1.8 weeks, range: 32-39) (p=0.04).

Gender distribution did not differ between Group 1a (M/F=6/7) and Group 2a (M/F=2/4) (p=0.63) or Group 1b (M/F=21/11) (p=0.31). It also did not differ between Group 2a (M/F=2/4) and Group 2b (M/F=7/1) (p=0.54).

Body weight did not differ between Group 1a (2720 ± 613 g, range: 1500-4000) and Group 2a (3290 ± 185 g, range: 2000-7000) (p=1.0) or Group 1b (3029 ± 1032 g, range: 1500-5700) (p=0.55). It also did not differ between Group 2a (3290 ± 185 g, range: 2000-7000) and Group 2b (3100 ± 871 g, range: 2100-4400) (p=0.60).

Age at initiation of PN was lower in Group 1a (19.7 ± 41.8 days, range: 1-155) than in Group 2a (31.5 ± 38.9 days, range: 3-100) (p=0.03), but was not different from that seen in Group 1b (38.3 ± 57.1 days, range: 2-210) (p=0.14). Age at initiation of PN was higher in Group 2a (31.5 ± 38.9 days, range: 3-100) than in Group 2b (24.1 ± 32.3, range: 2-90) (p=0.01).

The duration of PN was longer in Group 1a (34 ± 37 days, range: 5-143) than in Group 1b (13 ± 10 days, range: 3-47) (p=0.01). It was longer in Group 2a (146 ± 148 days, range: 27-400) than in Group 1a (34 ± 37 days, range: 5-143) (p=0.02) or Group 2b (14.0 ± 5.9 days, range: 7-27) (p=0.002).

PNAC developed later in Group 2a (42.0 ± 24.6 days, range: 11-79) than in Group 1a (9.0 ± 8.3 days, range: 1-31) (p=0.02).

Duration of PNAC did not differ between Group 1a (17.7 ± 21.3 days, range: 2-68) and Group 2a (33.2 ± 29.9 days, range: 7-63) (p=0.27) when the exitus cases were excluded.

Lipid dosage was higher in Group 1a (3.5 ± 0.7 g/kg/day, range: 2-4.3) than in Group 1b (3.45 ± 0.54 g/kg/day, range: 2-4.1) (p=0.001) or Group 2a (2.2 ± 0.4 g/kg/day, range: 2-3.1) (p=0.01). Lipid dosage was higher in Group 2a (2.2 ± 0.4 g/kg/day, range: 2-3.1) than in Group 2b (1.3 ± 0.5 g/kg/day, range: 0.5-2.0) (p=0.001).

The dosage of protein did not differ between Group 1a (2.4 ± 0.7 g/kg/day, range: 1.6-4.8) and Group 1b (2.3 ± 0.3 g/kg/day, range: 1.8-3.4) (p=0.05). The dosage of protein was higher in Group 2a (2.6 ± 0.5 g/kg/day, range: 1.8-3.1) than in Group 1a (2.4 ± 0.7 g/kg/day, range: 1.6-4.8) (p=0.01) or Group 2b (2.3 ± 0.9 g/kg/day, range: 1.0-3.3) (p=0.001).

The dosage of dextrose was higher in Group 1b (8.5 ± 2.5 g/kg/day, range: 6-16) than in Group 1a (8.4 ± 2.6 g/kg/day, range: 5.5-14.4) (p=0.001). The dosage of dextrose was higher in Group 2a (10.7 ± 3.3 g/kg/day, range: 6.2-16) than in Group 1a (8.4 ± 2.6 g/kg/day, range: 5.5-14.4) (p=0.01) or Group 2b (8.9 ± 1.0 g/kg/day, range: 7.6-10.8) (p=0.01).

The daily energy content of PN did not differ between Group 1a (75 ± 14 Cal/kg/day, range: 53.7-110.1) and Group 1b (79.5 ± 24.7 Cal/kg/day, range: 56.4-172) (p=0.98) or Group 2a (74.15 ± 15.7 Cal/kg/day, range: 50.7-99.1) (p=0.83). The daily energy content of PN was

Table I. Demographic and Clinical Data of Patients in the Study Groups

	Group 1 (January 2000 – May 2008)		Group 2 (June 2008 – May 2012)	
	PNAC (Group 1a)	CONTROL (Group 1b)	PNAC (Group 2a)	CONTROL (Group 2b)
Number of patients	13	32	6	8
PNAC rate (%)	14.6		13.0	
Gestational age (weeks)	36.0 ± 1.8	36.0 ± 2.5 [a]	35.0 ± 2.2	36.0 ± 2.3
Gender (M/F)	6/7	21/11	2/4	7/1
Body weight (g)	2720 ± 613	3029 ± 1032	3290 ± 185	3100 ± 871
Age at PN initiation (days)	19.7 ± 41.8 [b1]	38.3 ± 57.1	31.5 ± 38.9 [b2]	24.1 ± 32.3
Duration of PN (days)	34.0 ± 37.0 [c1]	13.0 ± 10.0	146.0 ± 148.0 [c2]	14.0 ± 5.9
PNAC diagnosis (day)	9.0 ± 8.3		42.0 ± 24.6 [d]	
Duration of PNAC (days)	17.7 ± 21.3		33.2 ± 29.9	
Lipid dosage (g/kg/day)	3.5 ± 0.7 [e1]	3.45 ± 0.54	2.2 ± 0.4 [e2]	1.3 ± 0.5
Protein dosage (g/kg/day)	2.4 ± 0.7	2.3 ± 0.3	2.6 ± 0.5 [f]	2.3 ± 0.9
Dextrose dosage (g/kg/day)	8.4 ± 2.6	8.5 ± 2.5 [g1]	10.7 ± 3.3 [g2]	8.9 ± 1.0
Energy content (Cal/kg)	75 ± 14	79.5 ± 24.7	74.15 ± 15.7	57 ± 10.8 [h]
Presence of sepsis	9/13	6/32	6/6 [i]	3/8

PNAC, parenteral nutrition-associated cholestasis; M, male; F, female; PN, parenteral nutrition
[a] Gestational age was lower in Group 1b than in Group 1a (p=0.04)
[b1] Age at PN initiation was lower in Group 1a than in Group 2a (p=0.03)
[b2] Age at PN initiation was higher in Group 2a than in Group 2b (p=0.01)
[c1] Duration of PN was longer in Group 1a than in Group 1b (p=0.01)
[c2] Duration of PN was longer in Group 2a than in Groups 1a and 2b (p=0.02, p=0.002)
[d] PNAC started later in Group 2a than in Group 1a (p=0.02)
[e1] Lipid dosage was higher in Group 1a than in Groups 1b and 2a (p=0.001, p=0.01)
[e2] Lipid dosage was higher in Group 2a than in Group 2b (p=0.001)
[f] Protein dosage was higher in Group 2a than in Groups 1a and 2b (p=0.01, p=0.001)
[g1] Dextrose dosage was higher in Group 1b than in Group 1a (p=0.001)
[g2] Dextrose dosage was higher in Group 2a than in Groups 1a and 2b (p=0.01, p=0.01)
[h] Energy content was lower in Group 2b than in Group 2a (p=0.04)
[i] Concomitant sepsis was a more significant comorbidity in Group 2a than in Group 2b (p=0.04)

lower in Group 2b (57.0 ± 10.8 Cal/kg/day, range: 38-73) than in Group 2a (74.15 ± 15.7 Cal/kg/day, range: 50.7-99.1) (p=0.04).

Sepsis was found to be associated in the cases of 9 (69%), 6 (18%), 6 (100%) and 3 (37%) patients in Groups 1a, 1b, 2a and 2b, respectively. Sepsis was not found to be a significant factor when Group 1a was compared with Group 1b (p=0.27) and Group 2a (p=0.94). However, the association of sepsis in all Group 2a patients was found to be a significant comorbidity when Group 2a was compared with Group 2b (p=0.04).

The origin of sepsis was a central venous catheter in 5 cases (55%) in Group 1a, in 4 cases (83%) in Group 1b, in all 6 cases (100%) in Group 2a and in 3 cases (37%) in Group 2b.

PNAC was managed in Group 1a and Group 2a respectively by cessation of PN (n=3 and n=1), cyclic PN (n=1 and n=1), ursodeoxycholic acid (n=2 and n=5), phenobarbital (n=1 and n=1), enteral feeding (n=4) and cessation of lipid transfusion (n=1).

The total mortality rate of PNAC was 37% (38% in Group 1a and 33% in Group 2a). All of these patients had sepsis concomitantly.

Discussion

PNAC is the most common hepatobiliary complication of PN. The pathophysiology of PNAC is still obscure; it is possibly multifactorial[2,17,18]. In the present study, infants with pediatric surgical disease who received

two different PN regimens during a 12-year period have been evaluated retrospectively for the development of PNAC.

The incidence of PNAC in newborns has been reported to be 14-60%[4-7]. The incidence in this study was found to be lower (14.1%) and was not affected by different regimens and slight differences in the composition of PN solutions.

It has been reported that PNAC is usually encountered in newborns with low gestational age and low birthweight and is not affected by gender[19-21]. The incidence of PNAC has been reported to be 50% and 10% in newborns with birthweights lower than 1000 g and above 1500 g respectively. In the present study, the mean gestational age was 35 weeks and the mean birthweight 3000 g in patients developing PNAC. The premature and low gestational age newborns had been treated in another neonatal ICU in our institute; the patients with pediatric surgical pathologies were born around the full term of gestation. The low PNAC incidence (14.1%) may be due to the higher proportion of mature, normal-birthweight infants in the present study. Gender seemed to have no effect on PNAC incidence, as previous reports have also indicated[19-21]. However, a reliable conclusion about the effect of gender cannot be derived from our series because of the limited number of cases in some groups.

The incidence of PNAC may be expected to be higher when PN is initiated at a younger age, due to hepatic immaturity. Interestingly, the age at PN initiation was lower in Group 1a than in Group 2a of the present study. However, this did not affect the incidence of PNAC in either of the PN protocols. This may be due to the delayed admission of Group 2a patients with different primary pathologies.

PNAC has been reported to be associated with receiving PN for longer than 60 days[5,20-25]. In the present study, PNAC was found to be associated with longer PN utilization periods in the new regimen, with a mean duration of 42.0 ± 24.6 days. It is reasonable to conclude that the duration of PN is associated with a higher risk of developing PNAC in pediatric surgical infants. PNAC is not expected to develop over a short period of PN usage. However, early development of PNAC (at 9.0 ± 8.3 days) was encountered in Group 1 patients in the present series. It had previously been reported that PNAC could develop as early as the 23rd day of PN[26].

Higher lipid concentration in the PN solution has been reported to be associated with increased risk of PNAC[27-30]. On the other hand, 1 g/kg/day and 2-3 g/kg/day lipid dosages produced similar PNAC incidences in another study[31]. In the present study, PNAC patients in Group 1 received higher lipid concentrations but lower concentrations of protein and dextrose than did those in Group 2. Therefore, higher lipid concentration was seen to be associated with the early development of PNAC in infants with pediatric surgical pathologies.

The length of time that PNAC lasts is directly related to the availability of oral feeding[6,32]. The duration of PNAC was found to be 29 days in a series of 27 patients[33]. In the present study, the duration of PNAC was similar in the two groups receiving different PN regimens. This observation may be due to the prompt commencement of various measures of treatment, including enteral feeding, in all patients with PNAC in our study.

Different protein contents of PN did not affect the development of PNAC in a group of 50 premature newborns with low birthweight (n=50)[34]. In another study, higher protein concentrations in PN solution resulted in earlier development of PNAC[35]. In contrast to this result, PNAC developed later in patients who received PN with higher concentrations of protein in our study (Group 2a). However, a significant conclusion regarding the effect of protein concentration on the development of PNAC could not be derived from that finding since the lipid and dextrose concentrations were not similar in the groups compared in our study.

Dextrose is not itself hepatotoxic; however, increased amounts of carbohydrates increase insulin secretion. Insulin stimulates enzymes that take part in the synthesis of fatty acids in the liver. The result is fatty liver, oxidative stress and consequent liver injury[36,37]. It appears that a higher dextrose concentration had no adverse effect on the development of PNAC in the present study, due to the delayed development of PNAC in patients receiving a greater amount of dextrose.

It has been reported that PN with a high caloric content can cause liver injury due to fatty liver and the resultant oxidative stress, which is produced by increased lipid and carbohydrate concentrations [21,22,36,37]. PN with a lower energy content was associated with a PNAC-free outcome in the patients in our series who received the newer PN regimen. A lower caloric content-PN solution contains lower concentrations of lipids and carbohydrates and may protect the liver from injury.

Sepsis has been considered one of the precipitating factors in the development of PNAC. PNAC was found to have developed mainly through bacterial infection in newborns who received 7-day PN treatment[7]. The incidence of association of PNAC and sepsis has been reported to be 32% in surgical newborns.[19] The incidence of sepsis in patients with and without PNAC has been found to be 80% and 34% respectively[38]. Sepsis is an important cause of death in PNAC patients. It also has the effect of increasing the inflammatory response in the liver[18,39]. Therefore, sepsis may play a role not only as a precipitating but also an aggravating factor in PNAC pathogenesis. The presence of concomitant sepsis was found significant in the development of PNAC in the more recent group (Group 2a) of patients in our study. PNAC developed later and persisted longer in this group. Therefore, in the present study, sepsis was a complication of the central line, kept in place for prolonged PN treatment, rather than a precipitating factor.

The key step in the treatment of PNAC is eliminating PN dependence and feeding the patient by the enteral route as early as possible. Cycling parenteral nutrition, UDA, phenobarbital, lipid-free parenteral nutrition and omega-3 rich lipid solutions can be also used. Recent studies have not confirmed the protective effect of cholecystokinin (sincalide) against PNAC[40,41]. A conclusion could not be derived from the present study regarding the options for treating PNAC because of the limited number of cases treated in line with the above-mentioned modalities.

Two different regimens resulted in similar PNAC rates (13%) in the PN treatment settings discussed here. Initiation of PN at an earlier age and prolonged PN treatment were found to increase the possibility of PNAC.

The lipid, protein and carbohydrate contents of PN solution affect the time at which PNAC occurs. The use of a PN solution with a high caloric content and high lipid concentration may play a role in the development of PNAC. Sepsis usually appears as a concomitant disease, most often resulting from prolonged PN treatment. A lower lipid concentration in the PN solution is much safer, since it may delay the development of PNAC. PNAC should be detected as early as possible and treated promptly. Enteral feeding is the most effective method of managing PNAC.

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