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Evaluation of parenteral nutrition-associated liver disease in surgical infants for necrotizing enterocolitis

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Abstract

The purpose of this study was to determine the factors associated with parenteral nutrition-associated liver disease (PNALD) in infants who underwent surgery for necrotizing enterocolitis (NEC) and followed up the postoperative outcomes for long term parenteral nutrition (PN).

This study included a retrospective review of 87 infants with NEC and managed surgically from July 2007 to May 2017 at the Children's Hospital, Chongqing Medical University. Clinical data and procedure information were collected and analyzed.

Among the infants included, 16.1% of patients developed PNALD. Multivariable logistic regression analysis revealed progressive clinical deterioration (OR, 5.47; 95% CI, 1.10–26.96; $P = .037$) was independent risk factor for PNALD whereas congenital heart disease (OR, 0.068; 95% CI, 0.008–0.55; $P = .012$) presentation served as a protective factor.

The current data suggested the distinct disease process for cardiac patients with NEC, which might help in the prevention and treatment of PNALD for patients with NEC.

Abbreviations: CHD = congenital heart disease, CI = confidence interval, CNEC = cardiogenic NEC, CRP = C-reactive protein, EN = enteral nutrition, IF = intestine failure, LOS = length of stay, NEC = necrotizing enterocolitis, OR = odds ratio, PN = parenteral nutrition, PNALD = parenteral nutrition-associated liver disease.

Keywords: congenital heart disease, necrotizing enterocolitis, parenteral nutrition, parenteral nutrition-associated liver disease

1. Introduction

Advances in parenteral nutrition (PN) have improved the management level for premature critically ill infants, which is often required to maintain their nutrition status and support growth. Accordingly, a common complication of parenteral nutrition administration, parenteral nutrition–associated liver disease (PNALD) might become common, which is characterized by cholestasis, steatosis, and can progress to liver failure that causes significant morbidity.[1,2,3] PNALD is especially common in infants diagnosed with NEC, who received prolonged courses of PN.[4,5] PNALD may cause cirrhosis, portal hypertension, and end-stage liver disease. PNALD is reversible after discontinuing PN in the majority of patients.[6] In a cohort study of 78 children with intestine failure (IF), the mortality rate among those with cholestasis (direct bilirubin concentration ≥2 mg/dL) was close to 80% compared with 20% in those without cholestasis.[7]

Although components of PN solution (either excess or lack of certain nutrients), the duration of PN, short bowel syndrome (SBS), prematurity, timing of enteral nutrition (EN), infections

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and endotoxin-induced liver injury have been postulated as potential causes of PNALD,[8,9,10] its etiology remains unclear. No unifying theory has been put forward to explain all the features of PNALD. Previous reviews have demonstrated that patients with NEC are at a greater risk for development of PNALD.[11]

We conducted a cohort study to determine the incidence of PNALD over decades and further devised a meaningful risk assessment for development of PNALD in a subset of patients who underwent surgical treatment for NEC. Identification of these factors may assist with resolution of cholestasis before the development of parenteral nutrition–associated liver disease in this patient population.

2. Methods

2.1. Patients

A retrospective review of the hospital-based cohort for infants with NEC from July 2007 and May 2017 was performed at Children's Hospital of Chongqing Medical University with the approval of the institutional review board (No. 38 of ethical review (postgraduate); March, 2019). Entry criteria for this study were infants with a diagnosis of NEC who underwent surgical procedure during the study period. Surgical therapy was defined as either exploratory laparotomy (with or without intestinal resection) or surgical placement of peritoneal drains. Exclusion criteria were

(1) evidence of abnormal liver biochemical testing before surgery;
(2) acute pulmonary bacterial infection;
(3) gastrointestinal anomalies (aproctia, intestinal atresia, or Hirschsprung disease);
(4) infants who died during acute NEC.
(5) no liver biochemical testing after 14 days of PN exposure, or
(6) incomplete follow-up data.

All infants with NEC were followed up in the hospital's outpatient clinic until at least 3 months of corrected age. If the patient developed PNALD, there was further follow up at the outpatient clinic. After institutional review board approval, records of patients who met inclusion criteria were retrospectively reviewed, including demographic information, physical examination findings, radiographic findings, ventilation status, diagnosis and procedure information, clinical management, laboratory data, blood culture results, length of stay (LOS), information of resected bowel segment, mortality, and discharge summaries. Maternal, prenatal, and intrapartum data, medication history (for both mother and child), mode of feeding (PN or EN), and newborn history before study entry were also abstracted from medical records.

The primary outcome measured was the risk factors for development of PNALD in infants. PNALD was defined as abnormal liver biochemical testing (serum direct bilirubin ≥2 mg/dL) with at least 14 days of PN exposure at the time of liver disease diagnosis and exclusion of other causes of neonatal cholestasis to explain the abnormal biochemical tests, such as choledochal cyst, biliary atresia, congenital infections, viral hepatitis, and metabolic diseases. Full enteral feeding was defined as the provision of ≥100 kcal/kg/day from enteral nutrition (EN) and demonstrating a mean weight gain of ≥15 g/day for 7 days, or being discharged after discontinuing PN. The clinical outcomes of

PNALD were defined as secondary outcomes, including enteral autonomy achievement, end-stage liver failure, etc.

2.2. Statistical analysis

Statistical comparisons were conducted using SPSS 22.0 software package (SPSS Inc, Chicago, IL). Factors available in clinical practice were selected from a large set of demographic, clinical, and laboratory variables. Continuous variables are shown as mean ± standard deviation (SD) when normally distributed and with equal variances. Categorical data are summarized as frequency counts and percentages and measured with the Chi-square or the Fisher exact statistic test. Variables with a P value ≤ .20 in the bivariate analysis or deemed clinically relevant were considered for inclusion in multivariable logistic regression models, with associations expressed as odds ratios (OR) to identify independent patient and institutional characteristics associated with PNALD development.

3. Results

3.1. Patient characteristics

Between July 2007 and May 2017, there were 143 preterm infants who underwent surgical intervention for NEC eligible for analysis. Fifty-six patients were excluded due to incomplete information (n=29) and intestinal malformation (n=27). Baseline demographic and clinical characteristics of the infants are shown in Table 1. The age at diagnosis was 23.31±20.61 days and about two-thirds of all of the patients were male, with a median gestational age and birth weight of 35.38 weeks and 2521.26 g respectively. Nine (10.3%) patients received vasopressor before NEC diagnosis. Twelve (13.8%) infants needed assisted ventilation. Most patients of the included infants (66, 75.9%) received enteral feeding before the diagnosis of NEC. The 16.1% of patients suffered PNALD.

We next performed the comparison of the baseline characteristics (Table 2) and clinical status (Table 3) of the infants according to the PNALD development or not. Lower gestational age birth weight and weight at diagnosis were more frequent in patients who developed PNALD ($P < .05$ for each), whereas congenital heart disease were less frequently reported in patients progressing to PNALD. Additionally, lower platelet count, albumin level and progressive clinical deterioration were also associated with PNALD (Tables 2 and 3). Statistically significant

Table 1

Baseline demographics and clinical characteristics for eligible Cohort (N=87).

Variables	
Male: female, n (%)	56:31 (64.4%: 35.6%)
Gestational age, week	35.38±3.81
Birth weight, g	2521.26±834.12
Bell's stage≥ stage 2, n (%)	59 (67.8%)
History of enteral feeding, n (%)	66 (75.9%)
Respiratory support, n (%)	12 (13.8%)
Probiotics, n (%)	34 (39.1%)
Age at diagnosis of NEC (days)	23.31±20.61
APGAR scores at 5 minutes	9.34±1.70
Congenital heart disease, n (%)	55 (63.2%)
Vasopressor use at enrollment, n (%)	9 (10.3%)

Table 2

Baseline demographics of eligible patient and preoperative variables (Chi-square test& Student's *t* test).

	PNALD (14)	No PNALD (73)	*P* values
Demographic factors			
Male: female	11:3	45:28	.364
Gestational age, week	33.23±3.12	35.8±3.81	.020
<=32, week, n (%)	4 (28.6)	17 (23.3)	.013
32.1–35.9, week, n (%)[*]	8 (57.1)	17 (23.3.)	
>=36, week, n (%)[*]	2 (14.3)	39 (53.4)	
Maternal factors			
Maternal age, years	29.00±5.45	28.82±5.07	.928
Steroid use during pregnancy	2 (18.2)	5 (10.4)	.840
History at Birth			
Cesarean delivery, n (%)	7 (50.0)	36 (49.3)	.963
Birth weight, g	2040.00±585.78	2613.56±845.82	.005
Very low birth weight infants (birth weight <1500 g), n (%)	3 (21.4)	9 (12.3)	.630
Low birth weight infants (birth weight <2500 g), n (%)	12 (85.7)	32 (43.8)	.004
Macrosomia (birth weight >4000 g), n (%)	0 (0.0)	1 (1.4)	1.000
APGAR scores at 5 minutes	9.57±0.79	9.29±1.84	.899
SGA infant, n (%)	2 (14.3)	6 (8.2)	.830
Feeding history			
Enteral nutrition before diagnosis of NEC, n (%)	9 (69.2)	57 (83.8)	.395
Received breast milk before diagnosis of NEC	3 (25.0)	13 (19.4)	.957
Parenteral nutrition before diagnosis of NEC	6 (42.9)	35 (48.6)	.693
Duration of PN (days)	129.6±89.5	68.7±41.3	.001
Characteristics at diagnosis of NEC			
Postnatal age at diagnosis, d	22.65±23.86	23.44±20.11	.759
Weight at diagnosis, g	1078.99±1186.60	1283.02±1427.38	.199
Bell stage≥ II	11 (78.6)	48 (65.8)	.530
Antibiotic use on day of diagnosis of NEC	10 (74.1)	65 (89.0)	.184
Probiotics, n (%)	7 (50.0)	27 (37.0)	.361
Vasopressor use at enrollment, n (%)	1 (7.1)	8 (11.0)	1.00
Respiratory support, n (%)	3 (21.4)	9 (12.3)	.630
First platelet count (onset of symptoms) (10^9/L)	193.77±99.85	306.35±173.63	.016
First hemoglobin (onset of symptoms) (g/L)	127.62±32.71	130.31±34.50	.795
First white blood cell (onset of symptoms) (10^9/L)	11.71±11.46	10.18±5.03	.644
First procalcitonin (ng/ml, normal value: 0–0.5)	3.86±3.89	9.23±21.62	.518
First CRP (mg/L, normal value: 0–10)	22.69±29.16	23.38±43.41	.484
First albumin (g/L, normal range: 35–50)	25.89±4.56	30.71±5.93	.005
Transfusion preoperation, n (%)	4 (28.6)	34 (46.6)	.342
Congenital heart disease, n (%)	3 (21.4)	52 (72.2)	.001

[*] There is significant difference between these 2 groups.

effects were not found for any other demographic characteristics, maternal and birth information, medical and feeding histories, or surgical interventions (Tables 2 and 3).

3.2. Risk and predictive factors for PNALD

Independent predictors of PNALD by multivariable logistic regression analysis using forward selection in the full cohort are shown in Table 4. Infants with progressive clinical deterioration, defined as increasing of abdominal distention, vomiting and bloody stool, were more than five times more likely to achieve PNALD than infants without clinical deterioration (OR, 5.605; 95% CI, 1.113–28.217; *P*=.037). Furthermore, congenital heart disease significantly decreased the risk of PNALD development (OR, 0.059; 95% CI, 0.006–0.551; *P*=.013). The other factors, like gestational age, birth weight, weight at diagnosis, albumin at onset, platelet count at onset, and other surgical interventions were not statistically significant after adjustment for the aforementioned independent predictors.

3.3. Clinical outcomes of PNALD

Clinical outcomes at a median follow-up of 37 (6–172) months are summarized in Table 5. There were 10 deaths overall (15%). Of the 14 patients with PNALD, all were managed medically, 9 have achieved enteral autonomy after a period of home PN and reversed from the PNALD.

4. Discussion

NEC has been suggested to contribute to cholestasis caused by PN. Our study uniquely identified 2 independent predictors of PNALD in the infants following surgical therapy for NEC: congenital heart disease, and progressive clinical deterioration. Overall, 16.1% of the cohort developed PNALD, making it a common morbidity of infants undergoing surgical therapy for NEC. PNALD can be reversed in more than two-third of the infants when PN is stopped, and enteral autonomy can also be achieved in more than two thirds of the current patients.

Surgical features of patients who undergone surgery (Chi-square test & Student's *t* test).

	PNALD (14)	No PNALD (73)	*P*
Pneumatosis intestinalis, n (%)	5 (35.7)	19 (26.4)	.477
Pneumoperitoneum, n (%)	6 (42.9)	29 (39.7)	.827
Portal venous gas, n (%)	3 (21.4)	11 (15.5)	.878
Positive paracentesis, n (%)	0 (0.0)	11 (15.3)	.198
Progressive clinical deterioration, n (%)	8 (57.1)	19 (26.0)	.021
Postnatal age at operation, days	26.14 ± 25.90	26.80 ± 21.86	.644
Operative time (mins)	123.94 ± 39.15	122.43 ± 37.01	.890
Operative blood loss (mL)	26.29 ± 24.75	20.10 ± 22.25	.780
Transfused patients, n (%)	2 (85.7)	61 (83.6)	1.000
Bowel involvement, n (%)			
Distal ileum	5 (35.7)	18 (24.7)	.390
Distal ileum and colon	5 (35.7)	23 (31.5)	.758
Ascending colon	7 (50)	30 (41.1)	.537
Descending colon	2 (14.3)	28 (38.4)	.153
Extent of disease, n (%)			
Multifocal NEC	10 (83.3)	48 (94.1)	.516
Localized NEC	4 (100)	15 (78.9)	1.000
Panintestinal NEC	6 (75.0)	21 (77.8)	1.000
Large bowel resected, cm	0.00 ± 0.00 (n=0)	25.42 ± 14.69 (n=12)	–
Small bowel resected, cm	10.00 ± 5.00 (n=3)	13.88 ± 15.14 (n=17)	.671
Creation of jejunostomy	0 (0.0)	1 (1.4)	1.000
Creation of ileostomy	7 (50)	33 (45.2)	.742

The prevalence of PNALD is unchanged with the technology development, although various incidences were reported.[12,13] Direct comparison, however, must be made cautiously due to the different patient groups enrolled. The present incidence of PNALD of 16.1% is similar to that reported by other reports.[14,15] In contrast, the present incidence was lower when compared to the incidence reported in another report, which was as high as 71% in preterm infants with gastrointestinal problems.[13] The reason for the discrepancy between studies is not known but may be in part related to the difference in the length of PN and the differences in definition of PNALD. It is noteworthy that in our study, most patients received PN for longer than 30 days.

It is very useful to predict which patients with NEC managed surgically will go on to develop PNALD, although it is also challenging to identify these high-risk patients. As reported in previous studies, PNALD has been attributed to various risk factors, including prematurity, low birth weight, sepsis, gastrointestinal surgery, and duration of PN.[16,17,18] Low gestational age and low birth weight were also reported as risk factors in previous studies.[13,14,19] In the univariate analysis of current data several factors seemed to be associated with the development of

Multivariate models for the development of PNALD.

	OR	95%CI	*P*
Gestational age, week	0.945	0.631,1.416	.783
Birth weight, g	1.000	0.998,1.001	.647
Albumin (g/L, normal range: 35–50)	0.898	0.748,1.078	.247
First platelet count (onset of symptoms) (10^9/L)	0.999	0.992,1.006	.804
Congenital anomalies, n (%)	0.068	0.008,0.552	.012
Progressive clinical deterioration, n (%)	5.467	1.108,26.962	.037

Patient outcomes.

	PNALD (14)	No PNALD (73)	Total (n=87)
Achieved enteral autonomy	9	53	62
Deaths (overall)	3	7	10
Due to PN	1	3	4
Due to end-stage liver failure	2	0	2

PNALD, which may provide clues about the etiology of PNALD, although that did not remain significant in the multivariate model.

The factors related to improved outcomes included congenital heart disease, which was in contrast to previous studies, some of which found no association between congenital anomalies and development of PNALD,[13,14,19] other researches suggested the mortality of congenital heart disease (CHD)and NEC together is substantially higher than that with each disease alone.[20,21] Another investigation with a mixture of term and preterm infants is in keeping with the current findings,[22] which found lower morbidity and a trend towards decreased rate of death from NEC in CHD patients. The decreased risk of negative NEC-related outcomes in the context of cardiac disease suggests that NEC in infants with CHD may have a unique pathophysiology under the broad categorization of NEC. No consistent pattern of cardiac pathophysiology leading to NEC has been established in the literature. The finding of an association between CHD and decreased PNALD in surgical infants warrants further investigation.

In the current analysis, we found that progressive clinical deterioration of NEC, which mainly included increasing of abdominal distention, vomiting and bloody stool, was identified as main risk factor for development of cholestatic liver disease, associated with subsequent need for PN. Thus, it seemed that patients with progressive clinical manifestations of NEC were more likely to progress to PNALD. Clinical deterioration with disrupted intestinal integrity may potentiate the local inflammatory response and in turn increase the severity of NEC, and the need for prolonged PN. The surgical factors (pneumatosis intestinalis, portal venous gas, pneumoperitoneum, etc.) are associated with increased severity of NEC and consequently require prolonged duration of PN.[23] We did not find any associations of surgical factors with PNALD as our data did not support this relation in patients with NEC, although there was a trend towards association with some surgical factors in the PNALD group. This might be explained by the small number of patients, particularly in the PNALD group.

The use of the fish oil emulsion in PN is a relatively new therapy without well-defined criteria for initiation. Fish oil emulsion as source of lipids can effectively shorten the duration of cholestasis.[24,25] Unfortunately, the fish oil has not been administered in our institute, yet. Another concern was the material of central venous lines. Bis (2-ethylhexyl) phthalate (DEHP)-plasticized polyvinyl chloride (PVC) infusion sets could affect human fertility and increase the risk of PN-associated cholestasis and must be avoided during the administration of parenteral nutrition (PN).[26] Here in our institute, this material was abandoned for many years.

The present study should be interpreted with certain limitations in mind. First, data were collected locally from a single institution, the main limitations in our study are inherent to

retrospective reviews. Another limitation of this study is small sample size. Although we have performed multivariate regression analyses, controlling for confounders is less rigorous for retrospective analysis and limited samples than in randomized controlled trials, which may limit the generalizability of the results. The general PN protocols were performed in our hospital over a long period of time; therefore, there may have been many practice changes by neonatologists and pediatric surgeons, leading to different care practices between study patients, which can lead to variability in treatment and not reflect the outcomes from current treatment algorithms.

5. Conclusions

In summary, PNALD is a common morbidity and presents as early as 2 weeks after induction of PN among patients undergoing surgery for NEC. We noted the favorable outcomes for PNALD in the presence of CHD, which supports the notion that cardiogenic NEC (CNEC) should be considered in the NEC population. Further studies should be performed to assess the differences and characteristics of CNEC.

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Author contributions

Conceptualization: Chun Deng, chunbao guo.
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