Preterm Small for Gestational Age Infants Are Not at Higher Risk for Parenteral Nutrition–Associated Cholestasis

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Objective To assess if being small for gestational age impacts parenteral nutrition–associated cholestasis (PNAC) development.

Study design We reviewed all the very low–birth weight infants exposed to parenteral nutrition for >14 days from 1996 to 2006, comparing auxological and clinical data, as well as nutritional history, during the first 4 weeks of life of infants with cholestasis and control subjects.

Results Of 445 very low–birth weight infants, 55 had development of PNAC. Infants with cholestasis had lower birth weight and gestational age but similar birth weight z-score compared with infants without cholestasis, and they received a lower amount of enteral feeds (25.8 ± 20.7 vs 67.9 ± 33.0mL/kg, $P < .001$), a greater amount of intravenous glucose (10.6 ± 1.3 vs 7.5 ± 2.5g/kg, $P < .0001$), lipids (1.8 ± 0.4 vs 1.3 ± 0.5, $P < .0001$) and proteins (2.7 ± 0.5 vs 1.9 ± 0.7, $P < .0001$), and needed a higher number of days of fasting (13.2 ± 6.7 vs 6.5 ± 4.8, $P < .001$). Enteral intake between 0 and 21 days of life (OR 0.66; 95% CI 0.53, 0.81, $P < .0001$) and oxygen therapy (OR 1.05; 95% CI 1.01, 1.09; $P = .030$) were identified as the best independent predictors of PNAC.

Conclusions Enteral feeding remains the main factor for the prevention of PNAC, whereas small for gestational age infants do not have a higher risk of PNAC. *(J Pediatr 2010;156:575-9)*.

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Parenteral nutrition (PN) plays an important role in the neonatal intensive care unit, and it can be life saving for critically ill newborn babies who are unable to receive adequate enteral nourishment. However, exposure to PN is demonstrated as the main factor in the development of cholestasis in preterm infants. Several risk factors related to intravenous hyperalimentation have been implicated in the development of parenteral nutrition–associated cholestasis (PNAC), such as the total caloric overload, the quality of amino acid solutions, the cumulative amount of lipid infusion, the presence of excessive aluminium in the PN solution, and the high manganese intake with PN.[1-5] Moreover, sepsis, necrotizing enterocolitis (NEC), bowel surgery, and lack of enteral feeding were suggested as potential contributors to the development of PNAC.[6-10]

It has recently been suggested that being small for gestational age (SGA) is an independent risk factor for PNAC.[11] The aim of our study was to assess in our population of very low–birth weight (VLBW) infants, whether being SGA is one of the independent risk factors for PNAC.

Methods

We performed a retrospective review of all infants with birth weight ≤ 1500 g assisted in our neonatal intensive care unit (NICU) from January 1, 1996, to December 31, 2006, who received PN for more than 14 days and who were still alive at 28 days of life. PNAC was defined as direct bilirubin greater than 2.0 mg/dL persistent for at least 2 consecutive tests during the administration of PN, not associated with other known causes of cholestasis.[1,12-14] Infants with cholestasis caused by genetic or metabolic disorders, congenital infections, extrahepatic obstructions, or congenital gastrointestinal disorders requiring surgery were excluded from the study. In all infants who received PN, direct bilirubin level was tested weekly.

Auxological and clinical data, as well as a complete and detailed nutritional history, were collected in all infants during the first 28 days of life. Gestational age

AGA	Appropriate for gestational age
BPD	Bronchopulmonary dysplasia
BW	Birth weight
GA	Gestational age
IUGR	Intrauterine growth restriction
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PN	Parenteral nutrition
PNAC	Parenteral nutrition associated cholestasis
SGA	Small for gestational age
VLBW	Very low birth weight

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was determined by the best obstetric estimate on the basis of the first day of the last menstrual period, prenatal ultrasound, and postnatal physical examination. SGA infants were defined with the Italian intrauterine reference values as those whose birth weight z-score was below −1.28.[15]

Among the main morbidities, bronchopulmonary dysplasia (BPD) was defined according to the most recent definitions[16]; necrotizing enterocolitis (NEC) was diagnosed according to the criteria of Bell, and only infants with a grade above IIa were considered as affected[17]; sepsis was defined by positive blood or cerebrospinal fluid cultures and typical clinical signs. Duration of oxygen therapy, mechanical ventilation, antibiotic treatment, as well as mortality rate and length of hospital stay were also considered. The nutritional history included the number of days without any enteral intake during the first 28 days of life, as well as the amount of enteral and intravenous daily intakes.

Two separate NICU databases were used as information sources: a nutrition database recording details about parenteral and enteral feeding, and a neonatal database containing demographic details, antenatal and perinatal history, postdelivery status, neonatal diagnosis, procedures, therapies, complications, and main outcomes at discharge. Data from the 2 databases and a review of the single medical records were entered into a single study database for the retrospective analysis.

PN was started for all VLBW infants within the first 24 hours of life; progression of nutrient intakes was regulated with an electronic decision-support program developed by our unit. Nutritional guidelines provided that infants were started at 1 to 2 g/kg/d of protein (Trophamine 6%), and increased to achieve a maximum of 3.5 -4.0 g/kg/day within the first week of life. Intravenous lipids (Intralipid 20%) were started at 0.5 g/kg/d and increased to a maximum of 3.0 g/kg/d at day 7 of life. Glucose administration was started with an infusion of 6 g/kg/day and advanced to a maximum of 12 to 14 g/kg/d, according to the daily infant's glycemic tolerance. Caregivers, using a computer in the NICU, could confirm or modify the recommended dosages looking at the individual infant. PN was stopped when infants were able to tolerate approximately 120 mL/kg/day of enteral feeding and showed sustained growth, defined by at least 15 g/kg/day, during the last 72 hours. Enteral feeding was planned to start within the first 24 to 120 hours of life with mother's milk, or with pasteurized pooled premature human milk; subsequently, infants were fed their own mother's milk fortified with Eoprotin (Milupa, Milan, Italy) when an intake of 100 mL/kg was well tolerated, and never before day 14 of life. When there were difficulties in obtaining sufficient quantities of human milk, or a mother was not able to supply her own milk, infants were fed, partially or totally, with a preterm formula.

Statistical Analysis

Results are showed as mean ± standard deviation (SD) for the continuous variables, and as percentages for the categorical variables. The groups were compared by use of the Student *t* test for parametric data, and the Wilcoxon rank-sum test (Mann Whitney U test) for nonparametric data. Categorical variables were compared by use of the Fisher exact test.

Multivariate analysis was conducted by logistic regression to define the role of specific factors that may affect PNAC. All the variables significantly associated to PNAC after the univariate analysis were entered into the initial model. Backward stepwise selection was used to select the variables to enter in the final model with a significance level for the removal and the addition, respectively, of 0.3 and 0.2. A 2-tailed value of $P < .05$ was considered significant. Statistical analysis was performed with the Stata Statistical Software: Release 10 (Stata Corp LP, College Station, Texas).

Table I. Data at birth, morbidity rates, and therapies of infants with and without PNAC, during hospital stay

	PNAC (n = 55)	No PNAC (n = 390)	*P*
Gestational age (w)	27.4 ± 2.5	28.7 ± 2.3	<.001
Birth weight (g)	850 ± 274	1052 ± 238	<.001
Male/Female	32/23	175/215	.083
BW z-score	−0.82 ± 1.17	−0.60 ± 1.11	.175
BW z-score < − 1.28 (%)	17 (30.9)	112 (28.7)	.752
NEC (%)	8 (14.5)	13 (3.3)	.002
BPD (%)	10 (18.2)	19 (4.9)	.001
Sepsis (%)	31 (56.4)	98 (25.1)	<.001
Antibiotic therapy (n of cycles)	5.3 ± 3.3	2.4 ± 2.1	<.001
Mechanical ventilation (days)	30.1 ± 43.4	11.2 ± 18.5	<.001
Oxygen therapy (days)	59.4 ± 69.6	21.6 ± 36.3	<.001
Length of stay (days)	111 ± 55	69 ± 36	.002
Mortality rate (%)	11 (20)	5 (1.3)	<.001

Results

During the study period 445 VLBW infants who met the inclusion criteria were identified, and 55 of them (12.3%) had development of PNAC. The mean day of life at which cholestasis was detected was 27.3 ± 10.8. The diagnosis of PNAC was made in 6 (11%) infants during the fourth week of life, in 16 infants (29%) during the fifth week of life, and in 33 infants (60%) after the fifth week of life. The mean maximum value of direct bilirubin was 5.1 ± 1.7 mg/dL. The mean duration of PNAC was 28.3 ± 12.9 days.

Infants who had development of PNAC were significantly more immature and smaller than those without PNAC; the mean birth weight (BW) z-score was similar between the 2 groups, as well as the percentage of infants with a BW z-score below –1.28 (Table I). Infants with PNAC had a higher incidence of main morbidities, required a longer duration of mechanical ventilation and supplemental oxygen, and showed a longer hospital stay and a higher mortality rate than infants without PNAC (Table I). Infants with PNAC received a significantly lower amount of enteral nutrition from 0 to 14, 0 to 21, and 0 to 28 days of life and needed a longer period of fasting as compared with infants who did not have development of PNAC (Table II). The mean amount of intravenous protein, glucose, and lipids from 0 to 14, 0 to 21, and 0 to

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