

Original Communications

Parenteral Amino Acid and Metabolic Acidosis in Premature Infants

Pushkaraj Jadhav, MD; Prabhu S. Parimi, MD; and Satish C. Kalhan, MBBS, FRCP

From the Schwartz Center for Metabolism and Nutrition and Department of Pediatrics, Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio

ABSTRACT. *Background:* Aggressive parenteral nutrition (PN) including amino acids is recommended for low-birth-weight infants to prevent energy and protein deficit. Their impact on acid-base homeostasis has not been examined. *Methods:* We investigated the impact of dose and duration of parenteral amino acids, with cysteine, on acid-base parameters in 122 low-birth-weight infants. Premature infants ≤ 32 weeks, ≤ 1850 g, and receiving parenteral amino acids at 1.5 g/kg/d for an extended period (>24 hours), or 3 g/kg/d for a short (5 hour), extended (24 hour), or prolonged (3–5 days) duration were included in the study. Data were obtained at age 0–3 days ($n = 43$) or, when clinically stable, age 3–5 days ($n = 49$). Data from 30 infants, matched for birth weight and gestational age, receiving PN during the first 5 days after birth were also obtained. Acidosis was defined as pH

<7.25 . *Results:* Acidosis was evident in all infants between 2 and 5 days after birth. Infants with large patent ductus arteriosus (PDA) exhibited significantly ($p < .05$) lower pH early, had higher blood urea nitrogen levels (26 ± 9 vs 18 ± 8 mg/dL; $p < .05$), and had greater weight loss ($\sim 17\%$ of birth weight) when compared with infants without PDA. Gestational age, weight loss, and patent ductus arteriosus accounted for 65% of variance in acidosis. *Conclusions:* Low-birth-weight infants develop metabolic acidosis between 2 and 5 days after birth, irrespective of dose and duration of parenteral amino acid administration. Careful management of parenteral fluids and comorbidities may lower the incidence of acidosis and promote protein accretion. (*Journal of Parenteral and Enteral Nutrition* 31:278–283, 2007)

Low-birth-weight infants, although born appropriate for gestational age, consistently show postnatal growth restriction.^{1–3} Postnatal growth failure in premature infants has been attributed to protein and energy deficits accruing over the duration of the hospital stay.⁴ Therefore, greater emphasis has been placed on early aggressive nutrition care of these infants in order to prevent postnatal growth retardation. A number of investigators have suggested that parenteral nutrition (PN) should be initiated as early after birth as possible and that parenteral amino acids be administered at 3–3.5 g/kg/d in order to mimic protein accretion during fetal life.^{5–12} Only a few studies have examined the safety of early and aggressive administration of parenteral amino acids to low-birth-weight infants. A recent publication by te Braake et al¹¹ showed that prematurely born infants tolerated PN containing 2.4 g/kg/d of amino acids initiated soon after birth, without any significant change in acid-base status. In their study, the amount of parenteral amino acids provided was lower than the current recommendation,⁸ and acid-base parameters were only monitored once a day. The impact of other factors affecting the acid-base status in premature infants was not explored.

We examined the dose-response relationship between duration—short (5 hour), extended (24 hour), and prolonged (3–5 days)—and dose—1.5–3.0 g/kg/d—of parenteral amino acids on changes in acid-base parameters in premature infants. In addition, we examined the effect of acuity of illness and clinical morbidities on the above parameters, specifically in relation to age at initiation of PN. Data in the literature¹³ had shown that balanced (cation = anion) amino acid mixtures, because they are ionically balanced, do not cause acidosis *in vivo*. Therefore, we hypothesized that changes in acid-base status in premature infants will be the consequence of associated clinical morbidities, and that early initiation of parenteral amino acids will not affect their acid-base status.

MATERIALS AND METHODS

The present study was prompted by an anonymous complaint to the institutional review board (IRB), insinuating high incidence of “perceived acidosis” with early parenteral administration of amino acids at 3 g/kg/d. Prospectively obtained laboratory data from our published^{14–16} and unpublished physiologic studies of glutamine metabolism and that obtained from chart review of a matched case-control group were examined. The impact of duration (5 hours, 24 hours, and 3–5 days) of parenteral amino acids at 1.5–3 g/kg/d on acid-base homeostasis was evaluated.

Subjects and Study Design

Low birth weight (LBW) preterm infants ($n = 122$) ≤ 32 weeks’ gestation and birth weight ≤ 1850 g were

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Correspondence: Satish C. Kalhan, MBBS, FRCP, Department of Gastroenterology and Pathobiology, Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195. Electronic mail may be sent to sck@case.edu.

TABLE I
Clinical characteristics

	1.5 g/kg/d Extended*	3.0 g/kg/d		
		Short*	Extended*	Prolonged†
n	19	17	15	20
Duration of PN (h)	24	5	24	72–120
Birth weight (g)	1174 ± 274	1239 ± 312	1117 ± 247	1077 ± 300
Gestational age (wk)	29 ± 2	29 ± 2	29 ± 2	27 ± 2
SNAP*	11 (1–18)	12 (5–21)	11 (4–21)	12 (5–16)
Weight loss % (0–5 d)	10 ± 4	10 ± 6	8 ± 3	11 ± 4

Mean ± SD.

Infants received parenteral amino acids either at 1.5 g/kg/d or 3 g/kg/d for short (5 h), extended (24 h), or prolonged (3–5 days) duration.

*Median (25%–75%). From References 16–17.

†From Reference 18.

PN, parenteral nutrition; SNAP, Score for Neonatal Acute Physiology.¹⁷

included in the study. Infants with congenital anomalies or with birth asphyxia were excluded. All study protocols were approved by the IRB. The infants included were (i) all who were part of previously reported kinetic studies (n = 71; Table I)^{14–16}; (ii) another prospective group of infants receiving higher-dose (3 g/kg/d) amino acids between 0 and 3 days after birth (n = 21; Table II), and (iii) a control group matched for birth weight and gestational age (n = 30; Table II). The matched control group consisted of infants not participating in any study protocol and admitted to the neonatal intensive care unit within ±48 hours of the index case (ii) and matched for birth weight and gestational age. The details of the kinetic studies protocols have been reported.^{14–16} Briefly, preterm infants were randomized to receive parenteral amino acids either at 1.5 g/kg/d or 3 g/kg/d for 24 hours. Thereafter, they received amino acids either at 3 g/kg/d or 1.5 g/kg/d for short (5-hour) or extended (24-hour) duration. Infants were studied between 0 and 3 days or between 3 and 5 days of age. However, because there was no significant difference in their laboratory parameters, their data have been combined for analysis. An additional group (Table I) was given amino acids with and without glutamine

at 3 g/kg/d for a prolonged (3–5 days) period. Data in the early high amino acid group were collected between 3 and 5 days of age (Table II). Eight infants in this group developed clinical comorbidities and could not continue the study protocol (withdrawn), whereas the other 13 completed the study (completed). The control group (n = 30) was matched with the early high amino acid group and was born within 48 hours of the index cases. Their data were collected from the review of clinical records. They were receiving parenteral amino acids at 1.5–3.0 g/kg/d (2.1 ± 0.4; mean ± SD) as per the routine clinical practice of the primary neonatologist.

All decisions regarding clinical management, IV fluids, glucose, Intralipid, electrolytes, minerals, and trace elements in the PN, ventilatory support, use of vasopressor, etc were made by the primary physician, irrespective of participation of infants in the study protocols.

Data Collection

The data were obtained prospectively, except those from the matched control group, which were collected later. Severity of respiratory distress syndrome was graded independently by the pediatric radiologist. The

TABLE II
Clinical characteristics of early amino acids and control groups

	Early high amino acids*		Controls (n = 30)
	Completed (n = 13)	Withdrawn (n = 8)	
Birth weight (g)	1280 ± 283	1017 ± 250*	1027 ± 393
Gestational age (wk)	30 ± 1	27 ± 2*	27 ± 3
IMV (d)	9 ± 7	30 ± 17†	24 ± 10
Patent ductus arteriosus (PDA; n)	3	7	10
Small: large	2:1	1:6	6:4
Age at diagnosis (d)	3 ± 1	5 ± 3	4 ± 2
Indomethacin use (n)	1	2	2
PDA ligation	1	5*	6
Amino acid load (g/kg/d)	2.7 ± 0.3	2.6 ± 0.3	2.1 ± 0.4
Cysteine (mg/kg/d)	106 ± 15	105 ± 13	86 ± 20
Fluid intake (mL/kg/d)	104 ± 11	107 ± 12	130 ± 16
Weight loss (%)	12 ± 3	17 ± 5*	10 ± 3

Mean ± SD.

Early high amino acids: 3.0 g/kg/d administered within 24 hours after birth. Completed: continued with 3.0 g/kg/d for 3–5 days. Withdrawn: developed clinical complications and did not continue with this protocol.

*p < .05; †p < .01.

IMV, duration of ventilator support.

TABLE III
Effect of dose and duration of parenteral amino acids on acid-base status

	1.5 g/kg/d Extended	3.0 g/kg/d		
		Short	Extended	Prolonged
n	19	17	15	20
Duration of PN (h)	24	5	24	72-120
pH	7.30 ± 0.05	7.32 ± 0.04	7.27 ± 0.02	7.29 ± 0.03
PaCO ₂ (mm Hg)	43 ± 6	40 ± 12	44 ± 4	43 ± 5
Chloride (meq/L)	111 ± 6	103 ± 28	114 ± 4	104 ± 3
Bicarbonate (meq/L)	19 ± 3	18 ± 6	20 ± 2	17 ± 3
Anion gap	12 ± 6	12 ± 5	9 ± 3	18 ± 3
Blood urea (mg/dL)	18 ± 7	16 ± 7	17 ± 8	24 ± 5
Ammonia (μm/L)	ND	65 ± 30	76 ± 21	51 ± 7

Mean ± SD.

Infants received parenteral amino acids either at 1.5 g/kg/d or 3 g/kg/d for short (5 h), extended (24 h), or prolonged (3-5 days) duration. PN, parenteral nutrition.

duration of ventilator support (IMV), including the duration of oxygen supplementation, was recorded. Patent ductus arteriosus (PDA) was diagnosed by 2D-ECHO by the pediatric cardiologist and graded into small, moderate, or large PDA according to the ECHO findings. Daily weight was obtained and the percent weight loss during the first 3-4 days after birth was determined. Total IV fluids administered, energy intake, glucose load, Intralipid, amount of parenteral amino acids, and the amount of cysteine added to the parenteral nutrient mixture were recorded daily for the first 5 days after birth or for the duration of the study protocol. The chloride/acetate ratio in the PN was obtained. IV fluid (0.45 normal saline with heparin) administered to maintain the patency of the indwelling arterial lines (~12 mL/d) was not included in the calculation of total IV fluids.

The frequency of laboratory tests including the arterial blood gases was decided by the primary physician according to the clinical status of the infants. Generally, infants had their arterial blood gases monitored every 2-4 hours. Only arterial blood gas data (pH, PaCO₂, PaO₂) obtained daily during the first week after birth were collected. Venous and capillary blood gas parameters were not included in the data collection. Serum electrolytes and blood urea nitrogen were obtained daily starting on the second day after birth as per clinical practice. Anion gap [(Na + K) - (Cl + HCO₃)] was calculated from the data of serum electrolytes. Blood ammonia levels were determined only in study subjects receiving 3 g/kg/d of parenteral amino acids.

Statistical Analysis

Data are reported as mean ± SD. All blood gases obtained on a given day were tabulated, and data were averaged every 8 hours to calculate the 24-hour average of pH, PaO₂, and PaCO₂ for each infant and for the individual groups. For infants in the "prolonged" study group and those in the control groups, in addition to the daily average, composite averages were determined for each infant and for the entire group. Similarly, averages for each day and composite averages for serum electrolytes were determined. Nominal data were analyzed using sign test and ordinal data using

the Wilcoxon signed rank sum test. Analysis of variance was used to compare the data within and between the groups. A stepwise regression model was developed using pH on day 3 and day 4 as a dependent variable and a number of factors (birth weight, gestational age, weight loss during the first 5 days after birth, total amount of IV fluids administered, PDA, and the amount of cysteine added to PN) that might affect pH as independent variables. A 2-tailed *p* value < .05 was considered statistically significant.

RESULTS

Clinical characteristics of infants enrolled in the previously reported studies¹⁴⁻¹⁶ are summarized in Table I. Birth weight, gestational age, and the score of neonatal acute physiology (SNAP), an indicator of severity of acute illness, were not different among infants recruited in different study protocols. All infants lost approximately 10% of their weight during the first 5 days after birth.

The impact of amino acid load 1.5 g/kg/d vs 3.0 g/kg/d for a short (5-hour) extended (24-hour), and for a prolonged period (3-5 days) on acid-base parameters is displayed in Table III. An increase in parenteral amino acids to 3.0 g/kg/d for a shorter or an extended duration had no significant impact on pH. Similarly, infusion of amino acids at 3.0 g/kg/d for a prolonged period had no effect on arterial pH. Arterial PaCO₂, serum chloride and bicarbonate, anion gap, and blood urea nitrogen were not different between the study groups. The concentration of blood ammonia was within the normal range in infants receiving 3.0 g/kg/d amino acids.

We recruited 21 infants between 0 and 72 hours after birth to examine the effect of 3-5 days of parenteral amino acids (3 g/kg/d) with or without supplemental glutamine on glutamine and whole body protein metabolism (unpublished data). Their clinical characteristics, along with matched case controls, are shown in Table II. Birth weight, gestational age, SNAP score, magnitude of weight loss, and age when the tracer isotope studies were performed in the "completed" group were similar to our previous studies. Premature infants who were "withdrawn" from the study protocol for clinical reasons had lower birth weight (*p* < .05), lower gestational age (*p* < .05), and their weight loss

TABLE IV
Sequential changes in acid-base parameters of early high amino acid group and controls

	Day 1	Day 2	Day 3	Day 4	Day 5
Study (n = 21)					
Amino acid load (g/kg/d)	—	2.4 ± 0.7	2.9 ± 0.3	2.8 ± 0.4	2.6 ± 1.3
pH	7.33 ± 0.07	7.30 ± 0.05	7.26 ± 0.06	7.25 ± 0.05	7.23 ± 0.08
PaCO ₂ (mm Hg)	41 ± 8 (20)	41 ± 6 (18)	45 ± 5 (16)	43 ± 7 (14)	46 ± 9 (14)
Bicarbonate (meq/L)	22 ± 2	22 ± 2	20 ± 2	21 ± 3	21 ± 3
Chloride (meq/L)	110 ± 6	112 ± 5	114 ± 4	111 ± 5	109 ± 5
Anion gap	11 ± 4 (8)	12 ± 3 (23)	13 ± 1 (23)	12 ± 2 (23)	12 ± 2 (23)
Controls (n = 30)					
Amino acid load (g/kg/d)	—	1.5 ± 0.7	2.1 ± 0.6	2.5 ± 0.5	2.4 ± 0.8
pH	7.32 ± 0.06	7.30 ± 0.04	7.25 ± 0.05	7.24 ± 0.05	7.24 ± 0.03
PaCO ₂ (mm Hg)	41 ± 6 (30)	43 ± 7 (27)	47 ± 7 (23)	49 ± 6 (22)	48 ± 7 (18)
Bicarbonate (meq/L)	21 ± 6	22 ± 2	22 ± 3	22 ± 3	21 ± 4
Chloride (meq/L)	110 ± 3	112 ± 5	112 ± 6	112 ± 5	110 ± 5
Anion gap	11 ± 2 (21)	12 ± 3 (30)	12 ± 3 (30)	12 ± 2 (30)	12 ± 3 (30)

Mean ± SD.

during the first 5 days after birth was significantly higher ($p < .05$) compared with those who completed the study. There was no significant difference in birth weight, gestational age, and SNAP score between withdrawn infants and those in the matched controls.

Infants who were withdrawn had greater prevalence of PDA (70%), had large PDA according to the echocardiography findings, and 5/7 (71%) infants underwent surgical ligation for PDA. In addition, these infants required ventilator support for a prolonged period ($p < .01$) and had significantly higher weight loss ($p < .05$) during the first 5 days after birth. As per the study protocol, infants in the study group received a higher amount of amino acid load and consequently a higher amount of cysteine added to the parenteral amino acid solution (Table II).

Sequential change in acid-base parameters during the first 5 days after birth in the study group and matched controls is shown in Table IV. Because there were no differences in acid-base parameters among those who completed and those who were withdrawn from the study, the data were combined. Acid-base parameters obtained *after* the infant was withdrawn from the study were not included in the analysis. Infants included in the study showed a progressive decline in arterial pH, with nadir on day 5 after birth. Infants in the withdrawn group also showed a decrease in pH with age; however, the lowest pH was evident earlier (ie, on the third day after birth). Infants matched for birth weight and gestational age (controls) and receiving lower doses of parenteral amino acids, as ordered by their primary care providers, also demonstrated a similar change in arterial pH with postnatal age. There were no differences in PaCO₂, serum bicarbonate, serum chloride, and anion gap within and between the groups.

The concentration of blood urea nitrogen on day 5 was higher in infants included in the study (31 ± 17 mg/dL) compared with controls (15 ± 10 mg/dL; $p < .05$). However, blood urea nitrogen levels increased starting on day 2 ($p < .01$) in infants in the withdrawn group. There was no change in serum sodium levels with advancing postnatal age. IV fluids were increased in all the groups during the first 5 days after birth.

There were no significant differences in total volume of IV fluids administered between the groups.

Because a lower pH was evident at an earlier postnatal age in the withdrawn and control groups, we examined a number of clinical factors contributing to metabolic acidosis (Table II). Infants who were withdrawn had large PDA; nearly two-thirds of these infants underwent surgical ligation and had significantly greater weight loss during the first 3 days after birth ($p < .05$). Analysis of individual cases revealed that the nadir in pH corresponded to the diagnosis of large PDA and the use of bicarbonate to treat acidosis.

In order to identify potential factor(s) contributing to metabolic acidosis, we have constructed a model with pH on days 3 and 4 as dependent variable and incorporated all the factors that could potentially cause metabolic acidosis preceding days 3–4 as independent variables. Gestational age, large PDA, and weight loss accounted for 65% of variance in pH.

DISCUSSION

We show that all very-LBW infants developed acidosis (pH < 7.25) between days 3 and 5 after birth. Infants with moderate to large PDA developed acidosis earlier. The diagnosis of PDA coincided with higher blood urea nitrogen. A lower pH correlated with gestational age, large PDA, and the magnitude of weight loss during the first 72 hours after birth. Importantly, the dose or duration of parenteral amino acid and cysteine did not seem to affect arterial pH (acidosis).

Defects in urinary acidification, together with a number of other factors such as infections, hypotension, inappropriate administration of IV fluids, higher insensible water losses, and decreased tissue perfusion, contribute to metabolic acidosis in premature infants. In such a complex situation, it is difficult to ascertain whether parenteral amino acids worsen metabolic acidosis in premature infants. In this study, we examined the interaction between a number of factors to identify the potential contributors to acidosis, specifically, the impact of dose and duration of parenteral amino acids.

Infants included in the present study received crystalline amino acid solution (10% TrophaAmine; Braun

Medical Inc, Irvine, CA), providing a mixture of essential and nonessential amino acids, as well as taurine and a soluble form of tyrosine, *N*-acetyl-D-tyrosine. The majority were nonsalt amino acids, except lysine and cysteine, which were added, respectively, as acetate and hydrochloride salt. Although the titratable acidity, the amount of blood buffers consumed *in vivo* to titrate the infusate (pH 5.5) to a normal blood pH, was not determined in infants, Heird and colleagues¹³ showed that infants and children receiving amino acid mixtures with high titratable acidity did not become acidotic. Their data suggest that metabolism of cationic amino acids and resulting release of excess protons (H^+) may cause hyperchloremic metabolic acidosis, if it is not balanced by an equal proportion of metabolizable anionic amino acids. Thus, determination of cationic gap (cationic amino acids - anionic amino acids + acetate) may assist in determining whether there is an imbalance in the amino acid mixture. TrophAmine is a balanced amino acid solution containing 156 mmol/L of cationic amino acids (arginine, histidine, and lysine) and 155 mmol/L of anionic amino acids (glutamic acid and aspartate) plus acetate. Thus, the metabolic acidosis observed in the LBW infants could not be attributed to the "balanced" amino acid mixture administered.

Infants in the present study demonstrated a *normal* anion-gap metabolic acidosis with advancing postnatal age (nadir on days 4-5). Few limited studies have examined the reasons for such a metabolic acidosis. Sato and colleagues¹⁸ showed that low-birth-weight infants have a higher urinary pH, higher fractional excretion of bicarbonate, and most importantly lower urinary ammonium excretion rate persisting even on days 4-6 after birth. They suggested that insufficiency of ammonium excretion was the main cause of metabolic acidosis in the early neonatal period.¹⁸ The reported pH in their study on days 4-6 (~7.32) was significantly higher than that observed in the present study (~7.24). Approximately 50% (7/15) of the infants in their study received bicarbonate infusion to treat metabolic acidosis. Exclusion of infants who had been receiving indomethacin, receiving PN, or receiving ionotropic drugs in their study had led to the selection of infants without common clinical confounders. In contrast, we included all infants, irrespective of clinical comorbidities.

Metabolic acidosis in the present study occurred independent of the amount and duration of amino acid infusions and the dose of supplemental cysteine, suggesting that factors other than parenteral amino acids contribute to the development of acidosis. A recent study has shown that administration of 2.4 g/kg/d of amino acids was safe and did not result in changes in acid-base parameters.¹¹ Our data are robust in that we determined the dose-response relationship, examined sequential changes in blood gas and serum electrolytes in response to a higher (currently recommended) dose of parenteral amino acid for a prolonged period, and examined the impact of cysteine load and other comorbidities. We observed that infants with large PDA developed acidosis early (day 3), had significantly lower arterial pH, were given IV bicarbonate to treat acidosis, and required ionotropic drugs to maintain

normal blood pressure (withdrawn group: Table II). PDA becomes clinically manifest with improvement in pulmonary compliance. The associated "ductal steal" affects blood flow to vital organs, resulting in hypoperfusion.¹⁹ Onset of early acidosis coinciding with the diagnosis of PDA and higher concentration of blood urea nitrogen in the withdrawn group suggest renal hypoperfusion. We speculate that in premature infants, renal tubular immaturity, hypoperfusion, and hypotension, accompanied by clinical interventions used to treat PDA, may have resulted in a decrease in pH at an earlier postnatal age. Our model confirmed that gestational age, weight loss, possibly as a result of restriction of IV fluids, and PDA accounted for a large majority (~66%) of acidosis in premature infants.

The present study underscores the complexities involved in identifying the cause of metabolic acidosis in a rapidly changing clinical situation (ie, the preterm neonate in the intensive care unit). Because blood pH is a labile parameter influenced by clinical state and confounding complications (PDA, hypovolemia, etc) and equally important clinical interventions, it is difficult to identify the cause of change in pH. In fact, the investigating committee appointed by the IRB found it difficult to manage the large amount of clinical and laboratory data obtained in these studies and resolved to identify acidosis according to administration of bicarbonate by the clinician. They were not able to attribute bicarbonate administration to any identifiable clinical parameters. Only by performing a case-control analysis could we show that low-birth-weight infants develop relative metabolic acidosis in the first few days after birth irrespective of the amount of parenteral amino acids administered.

We conclude that non-anion gap metabolic acidosis is common in premature infants. Early recognition and management of PDA, prevention of excess water losses in conjunction with judicious fluid and electrolyte management, and balancing cysteine hydrochloride with an equimolar amount of base (acetate) could prevent metabolic acidosis. Such a strategy will result in provision of an optimal amount of parenteral amino acids to promote nitrogen accretion in LBW infants.

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