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ORIGINAL ARTICLE

Early amino acids and the metabolic response of ELBW infants ($\leqslant$1000 g) in three time periods

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Objective: To evaluate early amino-acid (AA) administration in extremely low birth weight (ELBW) infants over three time periods, beginning with the initiation of this strategy.

Study design: This was a retrospective study of ELBW infants between 2000 and 2007. Nutritional intake and laboratory results were monitored during the first 5 days of life. Growth rates and complications were followed until discharge.

Result: Infants were similar in birth weight (BW), gestational age (GA) and severity of illness. The age at initiation of AA decreased significantly over time. Age at weight nadir, return to BW and percent postnatal weight loss decreased in epoch 3. There were modest increases in blood urea nitrogen (BUN), but no significant metabolic disturbances were observed. Cholestasis was more prevalent in epoch 2.

Conclusion: AA administration within the first hours of life appears to be safe and beneficial for ELBW infants. Absent signs of renal dysfunction, a modest rise in BUN is consistent with the neonate's utilization of AAs for energy.

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Introduction

Before birth, the early fetus uses amino acids (AAs) for both energy and growth.[1–5] Without the provision of exogenous AA after delivery, the extremely low birth weight (ELBW) infant will become catabolic, losing as much as 1% of protein stores daily because of on-going proteolysis.[6] Despite an increasing body of literature that supports the provision of intravenous AA within hours of birth to prevent this proteolysis,[7–12] practices continue to vary across nurseries in the United States because of concerns about metabolic capabilities of the ELBW infant.

The specific mix of total parental nutrition (TPN), including AAs, is guided by routine metabolic monitoring during the first days of life and is tailored to the individual infant's needs. Neonatologists use blood urea nitrogen (BUN) as one measure of the infant's metabolic response to the AA infusion. Rising BUN concentrations are often interpreted as a sign of the infant's intolerance to AA rather than as an evidence of utilization,[1,5,13] triggering a reduction in the subsequent day's parenteral allowance and increasing the accumulating protein deficit initiated at the cutting of the umbilical cord.

The primary purpose of this study was to evaluate how ELBW infants responded biochemically to different concentrations of AA administered within hours of birth during three time periods.

Methods

This was a retrospective study of infants admitted to the neonatal intensive care unit at Kosair Children's and University of Louisville Hospitals. Approvals from the Institutional Review Board at the University of Louisville, the Norton Hospital Research Office and the University of Louisville Hospital Research Integrity Office were obtained before record review. Time periods were epochs 1 (1/1/2000 to 12/31/2001), 2 (1/1/2002 to 6/30/2004) and 3 (6/1/06 to 6/31/07). Both nurseries are attended by members of the same university faculty practice. Infants were included if they met the following criteria:

- BW $\leqslant$ 1000 g
- Admission to neonatal intensive care unit within 24 h of birth
- Receipt of total parenteral nutrition for $\geqslant$5 days
- Survival $\geqslant$7 days

Infants were excluded if they were noted to have major congenital anomalies or would require surgery within the first 5 days of life.

AA infusions (Trophamine) were initiated at 80 to 100 ml k day^{-1} and adjusted individually as needed. Over the three time periods, AA content increased from 1.5 to 2.5% to its current 4%. At the described infusion rates, AA intakes ranged from 1.2 to

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2.0, 2.0 to 2.5 and 3.2 to 4.0 g k day^{-1} in epochs 1, 2 and 3, respectively.

Demographic data included birth weight (BW), gestational age (GA), Apgar scores and medical complications: surfactant deficiency disease, patent ductus arteriosus, hypotension (mean arterial pressure low enough to require pharmacologic intervention). SNAPPE-II scores[14] were calculated. The use of medications, including artificial surfactant (Survanta (Ross Products, Columbus, OH, USA)), indomethacin, dopamine, dobutamine and insulin was tracked. Body weight and nutritional intake (all sources) were collected from the date of birth (or admission, if outborn) through the first 5 days of life. Laboratory data included high and low values for BUN, creatinine, glucose, sodium and potassium. Outcomes of interest included age at return to BW, prevalence of hyperglycemia (blood glucose >120 mg per 100 ml), use of exogenous insulin, postnatal weight loss and electrolyte disturbances. Data regarding longer-term outcomes (sepsis, cholestasis, length of stay and discharge anthropometrics) were also collected.

Data were analyzed by SPSS (v 14) using one-way analysis of variance for continuous variables and Fisher's exact test for categorical variables. Statistical significance was set at $P<0.05$.

Results

Descriptive data are summarized in Table 1. BWs, GAs, SNAPPE-II and 5-min Apgar scores were similar in the groups across all time periods. Antenatal steroids were more consistently provided in epoch 3 compared to epochs 1 and 2. Surfactant deficiency disease was significantly more common in epochs 2 and 3 compared to epoch 1. The prevalence of patent ductus arteriosus and hypotension were similar in all three epochs. Table 2 shows that total days of TPN were similar, but that the mean age at initiation of TPN (h) steadily decreased across all epochs ($P<0.001$). The age at weight nadir, the proportion of postnatal weight loss and the age at return to BW all decreased significantly by epoch 3. The prevalence of cholestasis was significantly higher in epoch 2 compared to epochs 1 and 3. Length of stay was longer and postconceptional age at discharge was later in epoch 2 compared to epoch 1. The presence of extrauterine growth restriction (weight for GA <3rd percentile) decreased significantly from epoch 1 to epochs 2 and 3.

Table 3 describes nutritional intake during the study period. Total caloric intake increased significantly across epochs ($P<0.012$) as did total AA intake ($P<0.001$). Non-protein energy was similar in epochs 1 and 2, but was significantly higher in epoch 3 ($P=0.002$).

Figures 1 and 2 show trends for BUN and glucose over the first 5 days of life. Mean values of BUN day of life (DOL) 1 to 3 shows statistically significant differences (epoch 1 vs 2). Additionally, there were significant differences (epoch 1 vs 3) on days 2 and 5. Differences in sodium, potassium and creatinine values were not remarkable and are not shown. Overall, glucose concentrations

Table 1 Descriptive data (mean ± s.d.)

	Epoch 1 2000–2001	*Epoch 2 2002–2004*	*Epoch 3 2006–2007*	P
N	70	98	20	
BW	756 ± 162	776 ± 157	741 ± 200	NS
HC	23.0 ± 2.0	23.1 ± 2.1	23.0 ± 1.8	NS
GA	26.2 ± 2.1	25.8 ± 1.9	26.0 ± 1.8	NS
SGA_W at birth[a]	10.0%	6.1%	15.0%	NS
SGA_{HC} at birth[a]	10.0%	5.1%	10.0%	NS
SNAPPE	36.9 ± 18.6	40.9 ± 19.0	45.8 ± 24.1	NS
APGAR-5	6.9 ± 1.8	6.7 ± 2.1	6.5 ± 2.2	NS
Antenatal steroids	64%	59%	95%	0.002[b]
Surfactant deficiency disease	86%	96%	100%	0.019[c]
PDA	73%	79%	75%	NS
PDA ligation	14%	20%	7%	NS
Hypotension	31%	46%	30%	NS

Abbreviations: BW, birth weight; GA, gestational age; HC, head circumference; NS, not significant; PDA, patent ductus arteriosus; SGA, small for gestational age; SGA_{HC}, HC <3rd percentile for GA; SGA_W, weight <3rd percentile for GA.
[a]Weight or head circumference <3rd percentile.
[b]Epoch 2 vs 3.
[c]Epoch 1 vs 2.

Table 2 Outcome data (mean ± s.d.)

	Epoch 1 2000–2001	*Epoch 2 2002–2004*	*Epoch 3 2006–2007*	P
Age at TPNi	22.4 ± 22.3	9.5 ± 12.2	4.6 ± 6.3	<0.001[a]
Days of TPN	25.8 ± 12.4	31.5 ± 26.9	25.2 ± 21.3	NS
Insulin	8.6%	3.2%	5.0%	NS
Age at weight nadir	4.9 ± 3.4	4.4 ± 6.2	2.9 ± 3.2	0.044[b]
% Weight change	−14.0 ± 7.7	−10.6 ± 6.2	−8.8 ± 5.9	0.001[b,c]
Return to BW	13.9 ± 6.3	10.7 ± 5.7	8.3 ± 5.0	⩽0.001[b,c]
Sepsis	27%	36%	10%	0.032[d]
Cholestasis	11%	26%	5%	0.030[c]
Max dBR	1.1 ± 1.6	2.7 ± 4.3	1.3 ± 3.2	0.002[c]
Survival (%)	90%	90%	95%	NS
LOS	83.3 ± 24.9	105.2 ± 55.5	83.4 ± 28.8	0.003[c]
GA at d/c	38.3 ± 2.7	40.9 ± 7.4	38.1 ± 3.4	0.008[c]
Weight at d/c	2168 ± 436	2799 ± 966	2541 ± 573	<0.001[c]
HC at d/c	32.4 ± 2.2	33.9 ± 2.9	32.1 ± 3.5	<0.015[c,d]
$EUGR_W$ at d/c[e]	57.1%	34.7%	25.0%	0.005[c]
$EUGR_{HC}$ at d/c[e]	10.0%	6.1%	10.0%	NS

Abbreviations: BW, birth weight; dBR, direct bilirubin; d/c, discharge; EUGR, extrauterine growth restriction (<3rd percentile for GA); $EUGR_{HC}$, HC <3rd percentile for GA; $EUGR_W$, weight <3rd percentile for GA; GA, gestational age; LOS, length of stay; Max, maximum; NS, not significant; TPN, total parental nutrition; TPNi, TPN initiation.
[a]All epochs.
[b]Epoch 1 vs 3.
[c]Epoch 1 vs 2.
[d]Epoch 2 vs 3.
[e]EUGR: weight or HC <3rd percentile for GA.

Table 3 Nutritional support during study period (mean ± s.d.)

	Epoch 1 2000–2001	*Epoch 2 2002–2004*	*Epoch 3 2006–2007*	P
Average total intake (cc k day^{-1})	141.5 ± 32.6	150.1 ± 31.3	129.3 ± 31.3	0.008[a]
Average total energy (kcal k day^{-1})	41.4 ± 10.2	45.5 ± 9.7	56.5 ± 13.4	<0.012[b,c]
Average total AA (g k day^{-1})	1.2 ± 0.4	1.8 ± 0.6	3.0 ± 0.7	<0.001[b,c]
Average non-protein energy (kcal k day^{-1})	36.7 ± 9.6	38.1 ± 8.8	44.3 ± 13.1	0.002[c]
% As TPN	97.1 ± 7.7	96.7 ± 9.8	98.3 ± 3.0	NS

Abbreviations: AA, amino acid; NS, not significant; TPN, total parental nutrition.
[a]Epoch 2 vs Epoch 3.
[b]Epoch 1 vs Epoch 2.
[c]Epoch 1 vs Epoch 3.

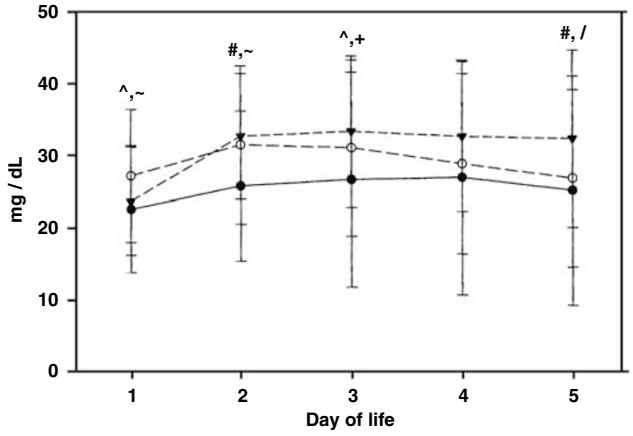

Figure 1 Serum BUN (mg/dL) in ELBW infants by epoch and day of life.

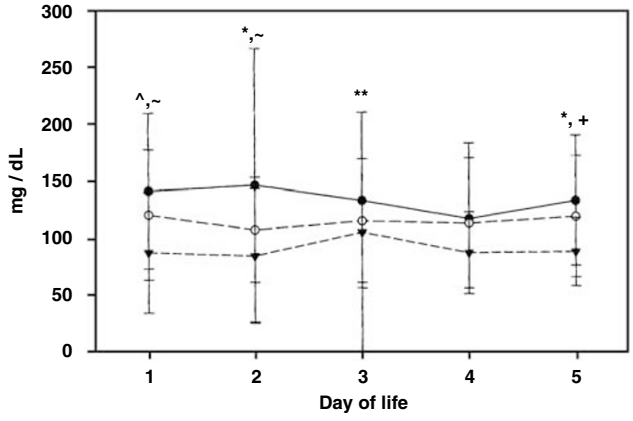

Figure 2 Serum Glucose (mg/dL) in ELBW infants by epoch and day of life.

were consistently lower in epoch 3 compared to epoch 1, although reaching statistical significance only on days 1, 2 and 5.

Figure 3 plots all BUN concentrations against the preceding day's AA intake. There was no demonstrable relationship between BUN and AA dose ($r^2 = 0.018$).

Table 4 compares infants with ($n = 34$) and without ($n = 153$) cholestasis. Overall, infants with cholestasis were smaller, less mature,

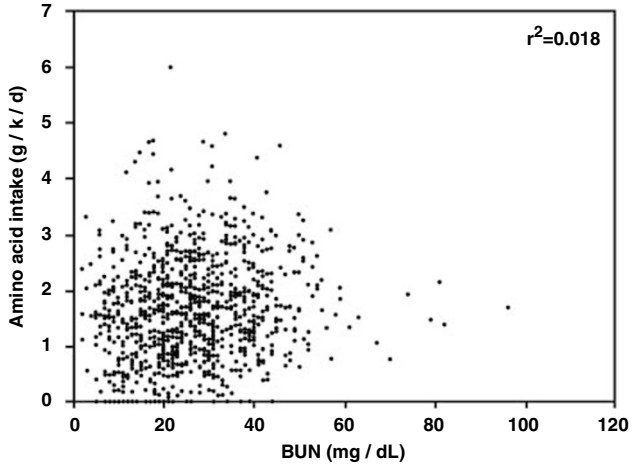

Figure 3 Correlation of serum BUN (mg/dL) with previous day's amino acid intake (g/k/d) in infants during the first five days of life.

had higher SNAPPE scores, and received more total days of TPN. There were no statistical differences in the age at initiation of AA, the amount of energy or AA intake in the first 5 days of life. Although not statistically significant, the proportion of infants found to be small for gestational age (SGA) at birth was higher in the cholestatic group (17.6%) compared with those without cholestasis (6.5%).

Discussion

These data add to the literature that supports the practice of providing AA solutions to ELBW infants within the first hours of life.[1,9–13,15–20] The fetus uses AAs for both growth and energy—providing parenteral AAs to an ELBW in the hours after birth is an extension of that metabolic process. The 4% AA infusion used in epoch 3 allows an infant to receive 3 g k day^{-1} by DOL 5, an amount that duplicates *in utero* growth.[8,11,21]

There were no significant metabolic disturbances in the first 5 days of life in our cohort. There were modest rises in BUN with essentially no change in creatinine as the AA dose increased. Consistent with the findings of Ridout *et al*.,[13] BUN levels in ELBW

Table 4 Characteristics of infants with cholestasis (mean ± s.d.)

	No cholestasis	Cholestasis	P
N	153	34	
BW (g)	787 ± 154	667 ± 172	<0.001
GA (weeks)	26.1 ± 1.9	25.2 ± 2.2	0.019
SGA at birth	6.5%	17.6%	0.082
SNAPPE	37.2 ± 18.9	52.1 ± 17.7	<0.001
APGAR-5	6.9 ± 2.0	6.0 ± 2.0	0.023
Age at TPNi (h)	14.7 ± 18.1	10.1 ± 15.3	NS
Days of TPN	24.3 ± 11.6	47.9 ± 38.4	0.001
Age at weight nadir (d)	4.6 ± 3.1	3.8 ± 3.7	NS
% Weight change	−12.1 ± 6.7	−9.9 ± 8.0	NS
Age at RTBW (d)	12.1 ± 6.2	9.6 ± 5.7	0.038
Max dir BR (mg per 100 ml)	0.6 ± 0.3	8.1 ± 4.4	<0.001
Sepsis	27.5%	41.2%	0.087
Hypotension	34.6%	58.8%	0.011
LOS (d)	89.5 ± 38.1	121.5 ± 66.8	0.025
Weight at d/c (g)	2492 ± 779	2700 ± 989	NS
HC at d/c (cm)	33.0 ± 2.7	33.5 ± 3.3	NS
Average volume (cc k day^{-1})	142.5 ± 31.0	155.2 ± 36.7	0.038
Average energy (kcal k day^{-1})	46.0 ± 11.3	41.8 ± 10.0	0.048
Average AA (g k day^{-1})	1.7 ± 0.8	1.7 ± 0.7	NS
Average TPN volume (cc k day^{-1})	138.5 ± 31.8	154.6 ± 37.3	0.011
Average TPN energy (kcal k day^{-1})	44.1 ± 11.0	41.7 ± 10.2	NS
Average TPN AA (g k day^{-1})	1.7 ± 0.8	1.7 ± 0.7	NS

Abbreviations: AA, amino acid; BW, birth weight; dir BR, direct bilirubin; d/c, discharge; GA, gestational age; LOS, length of stay; Max, maximum; NS, not significant; RTBW, return to BW; SGA, small for GA; TPN, total parental nutrition; TPNi, TPN initiation.

infants showed no correlation with AA intake. The ELBW infant that was a fetus just a few hours before utilizes AAs for both energy and lean mass production.[4,22] Studies of fetal AA oxidation suggest that higher concentrations of BUN may actually be evidence of effective utilization, not intolerance.[1,4,23] BUN reflects not only AA intake but also acuity of illness, renal function, hepatic synthesis and hydration status, thus, in the absence of signs of renal dysfunction (decreased urine output, very elevated BUN with creatinine >1.3 mg per 100 ml), a BUN in the range of 30 to 40 by itself should not be cause for decreasing AA infusions without further clinical evaluation of the patient.[13] It is now routine in our nurseries to reach a mean intake of 3 g k day^{-1} by the 5th day of life, an amount that is more than double that achieved in 2000 to 2001. Concomitantly, energy intake from non-AA sources increased even as infused volume decreased significantly. Thureen *et al*.[11] showed higher insulin concentrations in infants receiving AAs at 3 g k day^{-1} compared to those receiving 1 g k day^{-1}.[11] As glucose and lipid intakes were similar in the two groups, the difference in insulin concentrations was presumably due to the higher AA infusion. Similarly, it is possible that our infants in epoch 3 experienced better glucose tolerance with the higher AA intake.

Postnatal weight loss and age at return to BW also decreased significantly over time, but may have been influenced by the larger (but not statistically significant) proportion of infants that were SGA at birth in epoch 3. Across all study periods, the proportion of infants that showed extrauterine growth restriction (<3rd percentile) at discharge was reduced by half (57.1 vs 25.0%, $P = 0.004$).

In epoch 2, there was a higher prevalence of cholestasis compared to epoch 1. Upon further review of all infants with cholestasis, we found that these infants were of lower BW, earlier GA and more severe illness at birth. Overall, they received twice as many days of TPN as the non-cholestatic cohort and were over 1.5 times more likely to have experienced hypotension early in the postnatal period (58.8 vs 34.6%). Robinson and Ehrenkranz[24] and Baserga and Sola[25] have reported more cholestasis in infants with intrauterine growth restriction. Although there was not a statistically significant difference in the proportions of such infants in our data set, there was a trend to higher rates of cholestasis in SGA infants. However, our study was not designed to investigate this relationship.

A major limitation of this study was the absence of aminograms for our infants to analyze concentrations of specific AAs. However, Thureen *et al*.[11] showed that at 3 g k day^{-1} AA intake, plasma AA concentrations were similar to the second and third trimester fetal levels with no evidence of excessive aminoacidemia.[26–29]

Early AA administration appears to be a safe and beneficial practice for ELBW infants within the first hours of life. In the absence of signs of renal dysfunction, a modest rise in BUN is consistent with the neonate's utilization of AAs as a source of energy.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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