Received: 30 August 2021 | Revised: 22 November 2021 | Accepted: 24 November 2021

DOI: 10.1111/apa.16196

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Amino acid infusions in umbilical artery catheters enhance protein administration in infants born at extremely low gestational age

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Funding information
No external funding.

Abstract

Aim: It is challenging to provide extremely low gestational age neonates (ELGANs) with adequate protein supply. This study aimed to investigate whether amino acid (AA) infusion in the umbilical artery catheter (UAC) in ELGANs is safe and enhances protein supply and growth.

Method: A before and after study including infants born <27 weeks, treated in Uppsala, Sweden, during 2004–2007, compared those receiving normal saline/10% dextrose in water with those receiving AA infusion in the UAC. Data were retrieved from the Extremely Preterm Infants in Sweden Study, hospital records and the Swedish Neonatal Quality Register. Group comparisons, univariate and multivariate analyses were conducted.

Results: AA group (n = 41, females 39%) received on average approximately 0.3 g/kg/day more protein during the first postnatal week, compared to control group (n = 30, females 40%) (unstandardised coefficient (B) 0.26, p .001) but no difference was noted during 8–28 postnatal days. The type of infusion was not associated with growth variables. The incidence of neonatal morbidities and UAC-related thrombosis did not differ between the groups.

Conclusion: AA infusions in the UACs in ELGANs is safe and enhances protein supply during the first postnatal week. However, this practice is not associated with growth during the first 28 postnatal days.

KEYWORDS
amino acids, extremely low gestational age, growth, protein intake, umbilical artery catheter

Abbreviations: AA, amino acids; BPD, bronchopulmonary dysplasia; CI, confidence interval; DW10, 10% dextrose in water; ELGAN, extremely low gestational age neonate; GA, gestational age; HC, head circumference; IQR, interquartile range; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PDA, persistent ductus arteriosus; ROP, retinopathy of prematurity; SD, standard deviation; SDS, standard deviation score; UAC, umbilical artery catheter; UVC, umbilical vein catheter; ΔSDS, change in SDS.

1 | INTRODUCTION

Significant efforts have been made to improve the nutritional support of preterm infants in neonatal intensive care units (NICUs), in order to avoid cumulative nutritional deficits, reduce postnatal growth restriction and promote optimal long-term development.[1] Especially in the first week after birth, enhanced energy and macronutrient intake have been associated with improved neurodevelopmental outcomes and reduced incidence of neonatal complications in very low birthweight infants.[2,3] An adequate supply of parenteral amino acid solution (AA) has been shown to improve protein balance by increasing protein synthesis, improving the antioxidant defence system,[4] and potentially preventing a catabolic state and neonatal growth failure.[5,6] Despite the efforts, extremely low gestational age neonates (ELGANs) receive considerably less energy and protein than recommended, leading to postnatal growth failure.[7]

Umbilical artery catheters (UACs) are commonly used devices for monitoring of blood pressure, measurement of arterial blood gases and other indices, as well as infusion of fluids and medications.[8] However, UACs have also been linked to severe complications or even death.[8-10] Some fluid, commonly 0.25 normal saline, 0.5 normal saline, normal saline, or 10% dextrose in water (DW10),[8,11,12] with or without heparin to avoid clotting,[9] is infused through the catheter to maintain patency.[8,9,11,13] The variation in fluid stems from the concern regarding large sodium intake, dextrose-containing solutions contributing to hyperglycaemia or affecting blood-glucose determinations from the catheter and haemolysis from hypertonic solutions.[11,12] A randomised controlled study showed that infusion of AA solution and 0.5 normal saline flush in the UAC, as compared to 0.25 normal saline infusion and flush, has been associated with less haemolysis, allowed for greater early glucose nutrition while providing a nutritional benefit during the first postnatal week.[11] The authors did not find significant differences regarding short-term outcomes such as length of hospitalisation, discharge weight, mortality or serious morbidities such as severe intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), positive blood culture, persistent ductus arteriosus (PDA).[11]

This before and after study aims to evaluate the transition from normal saline/DW10 to isotonic AA UAC infusion, at the NICU of University Children's Hospital, Uppsala, Sweden, hypothesising that the latter enhances protein supply and growth, without increasing the incidence of neonatal morbidities or UAC-related complications. Protein supply and growth were the primary outcomes and the incidence of neonatal morbidities or UAC-related complications were the secondary outcomes of the study.

Key notes

- It is challenging to provide extremely low gestational age neonates (ELGANs) with adequate protein supply.
- Amino acid infusion in the umbilical artery catheter (UAC) is safe and enhances protein supply during the first postnatal week, compared to normal saline/10% dextrose in water. This practice does not affect growth during the first 28 postnatal days.
- Amino acid infusion in the UAC suggests a safe practice to increase protein supply in ELGANs.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a before and after non-experimental observational study that uses historical data of ELGANs to assess the effect of AA infusion in the UAC on protein supply, growth and neonatal morbidities. The before group (control group) included infants that received normal saline or DW10 infusion in their UAC (1 April 2004 to 30 September 2005). The after group (AA group) included infants that received AA infusion in their UAC (1 October 2005 to 31 March 2007).

2.2 | Inclusion and exclusion criteria

All ELGANs born at gestational age (GA) of <27 weeks, treated in Uppsala NICU, during the period 1 April 2004 to 31 March 2007, and who received UAC at birth were eligible for the study. Infants who did not survive the first week or were transferred to Uppsala NICU after 24 h of age were excluded from the study. No infants were discharged from Uppsala NICU before the UAC was removed. Infants with major congenital or chromosomal anomalies known to affect enteral function and, or, growth were excluded from the study. No infants had hydrocephalus. Infants who underwent surgical treatment for NEC during the first week were excluded from the analysis of protein supply and growth, as intestinal surgery was expected to interfere with enteral nutrient absorption, but were included in the analysis of neonatal morbidities.

2.3 | Data collection

Data on infant and maternal characteristics, as well as neonatal morbidities, were prospectively collected in the Extremely Preterm Infants in Sweden Study.[14] Data on nutritional intakes and growth outcomes were retrospectively collected from hospital records, as previously described,[7] and supplemented with data from the Swedish Neonatal Quality Register.[15] Internal controls of data entering were performed continuously and double-checked against original records. Nutrient intakes were calculated as mean daily intake, using the Nutrium software (Nutrium AB, Umeå, Sweden). A Swedish gender-specific growth reference was used to calculate standard deviation scores (SDS) for weight, length and head circumference (HC),[16] and a Canadian reference was used for infants born before 24 weeks GA.[17] Growth was calculated as changes in SDS (ΔSDS), for the time intervals 0–7 and 8–28 postnatal days.

The duration of mechanical ventilation and antibiotics were calculated as mean number of days, for each time interval, respectively. Bronchopulmonary dysplasia (BPD) was defined as the need for supplementary oxygen at 36 weeks of post-menstrual age; moderate if the oxygen need was <30% and severe if the infant needed ≥30% oxygen or positive pressure ventilatory support. Moderate retinopathy of prematurity (ROP) was defined as grade 1 or 2 and severe ROP as grade ≥3, with or without treatment. Moderate IVH was defined as grade 1 or 2, and severe IVH as grade 3 or 4. Sepsis was defined as a combination of clinical symptoms, C-reactive protein >15 mg/L and positive blood culture.

2.4 | Nutritional protocol

Volume-based prescription of nutrition was applied. All extremely preterm infants were fed exclusively with mother's own or donated breast milk, the first feeding given within one to two hours from birth. Enteral nutrition of 1ml breast milk every two hours was initiated during the first postnatal day, the rest of nutritional volume given as parenteral nutrition, at a total volume of approximately 90 ml/kg/day. Enteral feeding was progressively advanced and parenteral nutrition accordingly reduced, striving to reach full enteral nutrition of approximately 170 ml/kg/day within about 7 and 10 days. Total nutritional volume was adjusted, aiming not to exceed weight loss >15% during the transitional period of the first postnatal week and to achieve adequate growth thereafter.

The breast milk was fortified with Nutriprem (Nutricia Nordica AB, Stockholm, Sweden) after full enteral nutrition was reached, starting from 10 to 14 days. The fortification was increased stepwise with intervals of five to seven days up to three bags per 100 ml of breast milk. If satisfactory weight gain and linear growth was reached using two bags of Nutriprem, the third bag was not introduced to avoid constipation.

2.5 | Clinical practice of UAC use

Polyurethane-made, end hole, 3.5 French umbilical catheters (Vygon, Ecouen, France) were routinely inserted under sterile conditions in all extremely low gestational age infants, at birth, and were placed in a radiologically verified low position. The umbilical vein catheter (UVC) was used for the supply of parenteral nutrition and medications, and the UAC for continuous blood pressure monitoring and blood sampling for the determination of arterial blood gases and other indices. In order to maintain UAC patency, fluid was constantly infused with an infusion pump, commonly at a rate of 0.5 ml/h. Before September 2005, ELGANs with both UAC and UVC in place, received normal saline infusion in the UAC to maintain patency. Nine infants with unsuccessful UVC placement received DW10 in the UAC. In September 2005, this clinical practice changed and all ELGANs received the AA solution Vaminolac (Fresenius Kabi AB, Uppsala, Sweden) in the UAC, diluted to isotonicity (308 mOsmol) with sterile water, 3 parts of Vaminolac mixed with 2 parts of sterile water. This was done in an effort to achieve a higher total protein supply during the first postnatal week, potentially leading to better growth. Besides, the new infusion type was expected to reduce haemolysis and, or, false laboratory measurements, mainly of sodium and blood glucose, which can be affected by the infusion of normal saline and DW10, respectively.

During blood sampling, a volume of 2 ml of blood was first drawn in a syringe, then the blood sample was taken, and the 2 ml of blood

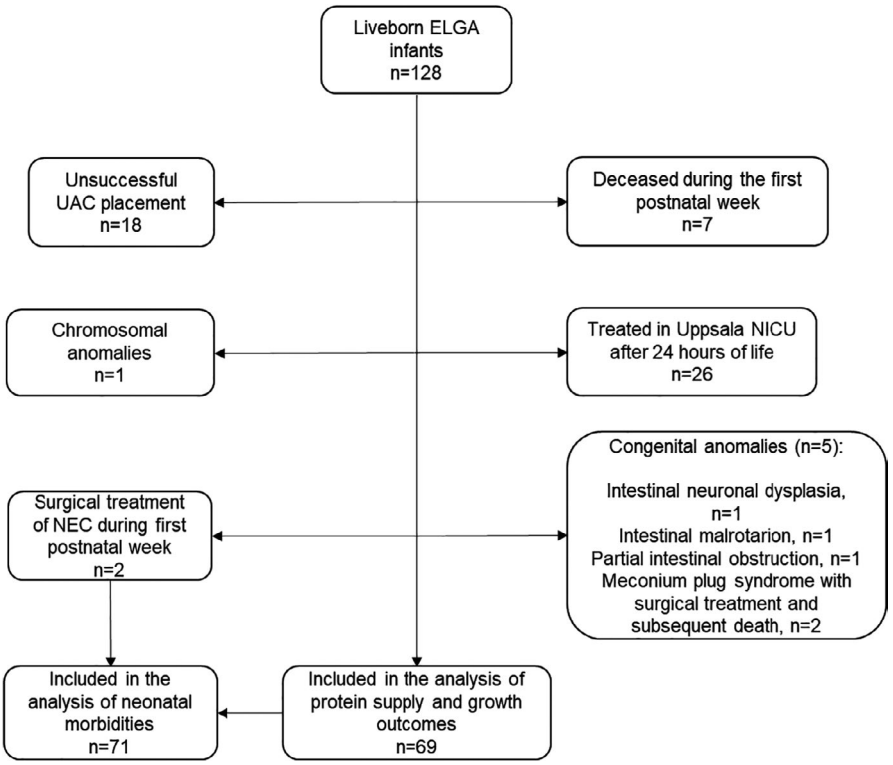

FIGURE 1 Flow chart presenting the selection of study participating infants. ELGA, extremely low gestational age; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; UAC, umbilical artery catheter

in the syringe were reinfused, followed by flushing the catheter with approximately 1 ml of normal saline. The blood sampling and flushing regimens remained unchanged during the whole study period. The UAC usually remained in place for a period of maximum seven days and was removed as soon as it was no longer needed, was occluded, or when catheter-related complication was suspected.

UAC-related thrombosis was detected through abdominal ultrasound conducted on clinical suspicion, such as renal failure or vascular compromise of the lower extremities. Upon thrombosis confirmation, UAC was removed and the progress of the thrombus followed clinically and with serial ultrasound examinations. No prophylactic antithrombotic medication or thrombolytic treatment was routinely administrated.

2.6 | Statistical analysis

Data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and as number and percentage for categorical variables. Group comparisons were made using two-tailed Student's *t* test or Mann-Whitney U test for continuous variables, and chi-squared test or Fisher's exact test

TABLE 1 Characteristics of study population and neonatal morbidity

	UAC with AA *n* = 41		UAC with normal saline/DW10 *n* = 30		
Variable	**Mean ± SD, Median (IQR) or *N*%**		**Mean ± SD, Median (IQR) or *N*%**		***p*-value**
Infant characteristics					
Gestational age, weeks	24.9	± 1.2	24.9	± 1.4	.90[c]
Female gender	16	39.0	12	40.0	.93[d]
Birthweight, grams	679.0	(559.0–819.0)	720.5	(548.0–897.8)	.75[e]
Birth length, cm[a]	31.9	± 2.8	31.9	± 3.1	.94[c]
Birth head circumference, cm[a]	22.9	± 1.6	22.8	± 2.2	.91[c]
Small for gestational age	9	22.0	4	13.3	.35 [d]
Apgar score					
1 min	6.0	(3.0–8.0)	6.0	(4.0–8.0)	.66[e]
5 min	8.0	(7.0–9.0)	8.0	(7.0–9.0)	.81
10 min	9.0	(8.0–9.0)	8.0	(7.8–9.0)	.30[e]
UAC, days	3.0	(2.0–4.0)	2.0	(1.0–4.0)	.28[e]
MV, days/week[b]	2.0	(0.9–5.4)	1.6	(0.3–5.3)	.31[e]
Antibiotics, days/week[b]	1.8	(0.0–2.0)	1.8	(0.0–1.8)	.64[e]
Maternal characteristics					
Age, years	30.2	± 6.5	29.3	± 6.4	.56[c]
BMI, kg/m^2[a]	25.8	(22.5–30.1)	24.3	(22.2–26.6)	.30[e]
Antenatal steroid administration	37	90.2	29	96.7	.39[f]
Multiple pregnancy	4	9.8	6	20.0	.30[f]
DM/gestational diabetes	1	2.4	2	6.7	.57[f]
Preeclampsia	8	19.5	5	16.7	.76[d]
Chorioamnionitis	3	7.3	4	13.3	.45[f]
Delivery method					
Vaginal birth	16	39.0	16	53.3	.23[d]
Caesarean section	25	61.0	14	46.7	
Smoking, cigarettes/day[a]					
1–9	5	12.8	4	13.8	0.92[e]
>10	2	5.1	1	3.4	

Abbreviations: AA, amino acid solution; BMI, body mass index; DM, diabetes mellitus; DW10, 10% dextrose in water; IQR, interquartile range; MV, mechanical ventilation; SD, standard deviation; UAC, umbilical artery catheter.

[a]Birth length was available for 69, birth head circumference for 70, mother's BMI for 62 and mother's smoking status for 68 out of 71 participating infants.

[b]For the time interval 0–28 postnatal days.

[c]*p*-value derived from *t*-test.

[d]*p*-value derived from chi-square test.

[e]*p*-value derived from Mann-Whitney *U* test.

[f]*p*-value derived from Fisher´s exact test.

TABLE 2 Fluid and nutrient supply in extremely low gestational age infants by type of UAC infusion, during 0–7 and 8–28 postnatal days

Variable	Unit	Day 0–7[a]				Day 8–28[b]			
		UAC with AA $n = 40$		UAC with normal saline/ DW10 $n = 29$		UAC with AA $n = 39$		UAC with normal saline/ DW10 $n = 27$	
		Median (IQR)		Median (IQR)	*p*-value	Mean ± SD or Median (IQR)		Mean ± SD or Median (IQR)	*p*-value
Total fluid	ml/kg/day	122.5	(114.3–130.8)	120.0	(111.0–128.0) .32[c]	167.3	(160.7–178.7)	169.3	(158.7–185.0) .68[c]
Total energy	kcal/kg/day	64.5	(59.3–71.8)	62.0	(57.5–66.0) .16[c]	116.0	(106.0–125.3)	116.3	(106.3–134.3) .92[c]
Proportion of enteral energy	%	59.0	(45.7–71.5)	64.0	(45.1–74.4) .62[c]	94.2	(86.3–98.8)	92.0	(86.2–98.3) .65[c]
Protein	g/kg/day	1.8	(1.7–2.0)	1.6	(1.3–1.7) <.001[c]	3.1	± 0.5	3.1	± 0.5 .73[d]
Carbohydrates	g/kg/day	8.4	(7.9–8.7)	7.8	(7.6–8.6) .15[c]	11.6	(11.2–12.1)	11.4	(10.6–12.6) .55[c]
Fat	g/kg/day	2.5	(2.0–3.2)	2.5	(2.0–2.9) .77[c]	6.1	± 1.0	6.3	± 1.1 .56[d]

Abbreviations: AA, amino acid solution; DW10, 10% dextrose in water; IQR, interquartile range; SD, standard deviation; UAC, umbilical artery catheter.

[a]Two infants excluded due to surgical treatment of necrotising enterocolitis (NEC) during the first week.

[b]Two infants excluded due to surgical treatment of NEC during the first week, and 3 infants deceased during 8–28 postnatal days.

[c]*p*-value derived from Mann-Whitney *U* test.

[d]*p*-value derived from *t*-test.

for categorical variables. The association of the type of UAC infusion with protein supply and growth outcomes was investigated through univariate and standard multiple linear regression analysis, including the pre-specified covariates GA, gender, baseline SDS of each growth outcome for each time interval, as well as duration of UAC, mechanical ventilation and antibiotics. In order to take into consideration the physiological weight loss during the first week, and the fact that the effects of nutrition on growth might vary by postnatal age, analyses were conducted separately for the periods of 0–7 and 8–28 postnatal days. The SPSS statistical software version 27.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses and the level of statistical significance was set at .05.

2.7 | Ethics

The study was approved by the Ethics Committee in Lund, Sweden, approval number (Dnr 42/2004).

3 | RESULTS

Out of 128 live-born ELGANs, 71 were included in the study, 30 in the control group and 41 in the AA group, as shown in Figure 1. No statistically significant differences were identified between the groups, regarding infant and maternal characteristics, although it should be noted that the median duration of UAC was 3 and 2 days for the AA and control group, respectively, as shown in Table 1.

Investigation of total fluid, energy and macronutrient supply during 0–7 and 8–28 postnatal days, presented in Table 2, resulted in a higher mean protein supply in the AA group, compared to the control group, during the first week (1.9 and 1.6 g/kg/day, respectively). Infants in the AA group and the control group received a median of 64.5 and 62.0 kcal/kg/day, *p* .16, during the first week, respectively.

Table 3 presents the unstandardised coefficients (*B*) and 95% confidence intervals (CIs) for the association of type of UAC infusion with protein supply and growth outcomes during the first postnatal week, derived from univariate and standard multiple linear regression analysis. AA group received on average 0.3 g/kg/day more protein during the first postnatal week, compared to control group (*p* .001). This finding remained statistically significant, even though slightly attenuated, after adjustment for potential confounders (*B* 0.26, *p* .001). GA and birthweight SDS were negatively associated with protein supply per kg (*B* −0.09, *p* .008 and *B* −0.11, $p < .001$, respectively). Moreover, the longer the UAC was in place, the higher was the protein supply (*B* 0.07, *p* .002).

The type of UAC infusion was not associated with weight, length and HC ΔSDS during the first week; neither was GA, gender, duration of mechanical ventilation and antibiotics. Infants with lower birthweight, length and HC SDS had significantly higher weight, length and HC ΔSDS, respectively, during the first week. Infants with longer duration of UAC showed a significantly lower weight

TABLE 3 Associations between protein intake (g/kg/day) and change in growth SDS (ΔSDS) by type of UAC infusion in extremely low gestational age infants during the first postnatal week

		Protein intake, $n = 69$[c]		Weight gain, $n = 68$[d]		Length gain, $n = 63$[e]		HC growth, $n = 64$[f]	
		B (95% CI) *p*-value		*B* (95% CI) *p*-value		*B* (95% CI) *p*-value		*B* (95% CI) *p*-value	
Variable	**Category or unit**	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]
Type of UAC infusion	AA versus normal saline/DW10	0.30 (0.13 to 0.48) .001	0.26 (0.12 to 0.40) .001	0.09 (−0.12 to 0.30) .40	0.11 (−0.09 to 0.30) .27	−0.09 (−0.51 to 0.34) .69	−0.05 (−0.45 to 0.36) .82	−0.01 (−0.23 to 0.22) .96	0.03 (−0.16 to 0.22) .76
Gestational age	weeks		−0.09 (−0.16 to −0.03) .008		−0.06 (−0.16 to 0.03) .18		−0.10 (−0.29 to 0.08) .27		−0.01 (−0.10 to 0.08) .83
Gender	male versus female		0.09 (−0.06 to 0.23) .25		0.12 (−0.08 to 0.33) .23		0.19 (−0.23 to 0.62) .36		0.11 (−0.10 to 0.31) .30
Birth SDS[g]	N/A		−0.11 (−0.17 to −0.05) <.001		−0.14 (−0.22 to −0.06) .001		−0.19 (−0.31 to −0.08) .002		−0.33 (−0.45 to −0.21) <.001
Duration of UAC	days		0.07 (0.03 to 0.11) .002		−0.07 (−0.13 to −0.01) .02		0.05 (−0.07 to 0.17) .38		−0.01 (−0.07 to 0.04) .71
Duration of mechanical ventilation	days		0.02 (−0.01 to 0.05) .20		−0.02 (−0.07 to 0.02) .35		−0.07 (−0.16 to 0.02) .12		−0.03 (−0.07 to 0.02) .24
Duration of antibiotics	days		0.00 (−0.03 to 0.03) .89		−0.02 (−0.06 to 0.02) .32		−0.01 (−0.09 to 0.06) .73		0.01 (−0.02 to 0.05) .49

Abbreviations: AA, amino acid solution; CI, confidence interval; DW10, 10% dextrose in water; HC, head circumference; N/A, not applicable; SDS, standard deviation score; UAC, umbilical artery catheter.

[a]Unstandardised coefficient (*B*) for type of UAC infusion, derived from univariate linear regression analysis.

[b]Unstandardised coefficient (*B*) for type of UAC infusion and confounding variables (gestational age, gender, birth SDS, duration of UAC, mechanical ventilation and antibiotics), derived from standard multiple linear regression analysis.

[c]Two infants were excluded due to surgical treatment of necrotising enterocolitis (NEC) during the first week.

[d]Two infants were excluded due to surgical treatment of NEC during the first week, and weight at one week was missing for one infant.

[e]Two infants were excluded due to surgical treatment of NEC during the first week, both birth length and length at one week were missing for one infant, birth length was missing for one infant, and length at one week was missing for four infants.

[f]Two infants were excluded due to surgical treatment of NEC during the first week, birth HC was missing for one infant, and HC at one week was missing for four infants.

[g]Adjustment for birthweight SDS in the analyses of protein intake and weight gain; adjustment for birth length SDS and birth HC SDS in the analyses of length gain and HC growth, respectively.

TABLE 4 Associations between protein intake (g/kg/day) and change in growth SDS (ΔSDS) by type of UAC infusion in extremely low gestational age infants during postnatal days 8–28

		Protein intake, $n = 66$[c]		Weight gain, $n = 66$[c]		Length gain, $n = 60$[d]		HC growth, $n = 62$[e]	
		B (95% CI) *p*-value		*B* (95% CI) *p*-value		*B* (95% CI) *p*-value		*B* (95% CI) *p*-value	
Variable	**Category or unit**	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]	**Crude**[a]	**Adjusted**[b]
Type of UAC infusion	AA versus normal saline/DW10	−0.04 (−0.28 to 0.19) .73	−0.04 (−0.27 to 0.19) .73	0.06 (−0.27 to 0.39) .71	0.08 (−0.22 to 0.38) .58	−0.44 (−0.95 to 0.07) .09	−0.32 (−0.80 to 0.17) .20	0.18 (−0.16 to 0.52) .30	0.22 (−0.10 to 0.54) .17
Gestational age	weeks		0.09 (−0.04 to 0.21) .18		0.32 (0.15 to 0.48) <.001		0.21 (−0.05 to 0.46) .11		0.18 (0.01 to 0.35) .04
Gender	male versus female		−0.10 (−0.35 to 0.14) .40		0.02 (−0.29 to 0.33) .89		0.17 (−0.34 to 0.67) .51		0.02 (−0.33 to 0.36) .91
Birthweight SDS	N/A		−0.01 (−0.10 to 0.09) .91		--		--		--
Baseline SDS[f]	N/A		--		−0.01 (−0.15 to 0.12) .85		−0.17 (−0.32 to −0.02) .03		−0.40 (−0.64 to −0.16) .002
Duration of UAC	days		0.06 (−0.01 to 0.14) .08		0.04 (−0.05 to 0.13) .38		−0.04 (−0.18 to 0.11) .62		−0.01 (−0.11 to 0.09) .84
Duration of mechanical ventilation	days		−0.02 (−0.07 to 0.04) .58		0.07 (0.00 to 0.14) .05		−0.03 (−0.15 to 0.08) .59		0.06 (−0.02 to 0.13) .14
Duration of antibiotics	days		−0.05 (−0.14 to 0.05) .34		−0.14 (−0.27 to −0.02) .02		−0.17 (−0.37 to 0.03) .10		−0.10 (−0.23 to 0.03) .14

Abbreviations: AA, amino acid solution; CI, confidence interval; DW10, 10% dextrose in water; HC, head circumference; N/A, not applicable; SDS, standard deviation score; UAC, umbilical artery catheter.

[a]Unstandardised coefficient (*B*) for type of UAC infusion, derived from univariate linear regression analysis.

[b]Unstandardised coefficient (*B*) for type of UAC infusion and confounding variables (gestational age, gender, birthweight or baseline SDS, duration of UAC, mechanical ventilation and antibiotics), derived from standard multiple linear regression analysis.

[c]Two infants were excluded due to surgical treatment of necrotising enterocolitis (NEC) during the first week, and three infants deceased during 8–28 postnatal days.

[d]Two infants were excluded due to surgical treatment of NEC during the first week, three infants deceased during 8–28 postnatal days, and length at one and four weeks of age was missing for six infants.

[e]Two infants were excluded due to surgical treatment of NEC during the first week, three infants deceased during 8–28 postnatal days, and HC at one and four weeks of age was missing for four infants.

[f]Adjustment for weight, length, or HC SDS at one week of age, in the analysis of weight gain, length gain and HC growth, respectively.

ΔSDS during the first week (*B* −0.07, *p* .02), and no association was observed regarding length and HC ΔSDS.

Investigation of the same associations shown in Table 3 for the period 8–28 postnatal days, presented in Table 4, showed that protein supply was not associated with the type of UAC infusion or any of the covariates included in the model. Infants with higher GA had higher weight ΔSDS (*B* 0.32, *p* < .001). Moreover, a negative association of the duration of antibiotics with weight ΔSDS was noted (*B* −0.14, *p* .02). Infants who were shorter at baseline showed a more profound length ΔSDS (*B* −0.17, *p* .03). Infants with higher GA and lower baseline HC SDS had better HC growth (*B* 0.18, *p* .04 and *B* −0.40, *p* .002, respectively).

As shown in Table 5, the incidence of short-term neonatal morbidities, namely BPD, ROP, IVH, sepsis and UAC-related thrombosis, and of PDA ligation and NEC surgery did not differ between the study groups.

4 | DISCUSSION

To our knowledge, this was the first study to investigate the effect of AA infusion to maintain UAC patency on protein supply and growth indices as the primary outcomes, during the first four postnatal weeks. The study confirmed the hypothesis that AA instead of normal saline/DW10 infusion in the UAC is associated with higher protein supply during the first postnatal week in ELGANs, without increasing the risk of neonatal morbidities or UAC-related complications. No association between the type of UAC infusion and any of the growth outcomes investigated, during the first 28 postnatal days, was observed.

Our findings were in line with previous results by Jackson et al. showing that AA infusion and 0.5 normal saline flushing of the UAC resulted in higher protein supply during the first week, as compared to 0.25 normal saline infusion and flush solution.[11] The AA solution was infused at a higher rate and concentration in infants weighing more compared to less than 1 kg and the flushing regimen was different between the groups,[11] rendering it not directly comparable to the study herein. In our study, the AA infusion rate and concentration in the exposure group, and the flushing regimen in both study groups were the same for all infants, potentially providing a clearer effect of the AA infusion itself. Moreover, the mean GA of participating infants was lower in our study than in the study by Jackson et al. (24.9 versus 27.0, respectively).

AA intake should be started as soon as possible after birth in preterm infants, and should be at least 1.5 g/kg/day on the first postnatal day, and 2.5–3.5 g/kg/day from postnatal day 2 onwards.[1] In our study, although AA infusion in the UAC seemed to increase protein supply, the recommended levels during the first postnatal week, considered necessary for positive protein balance of sufficient magnitude to promote actual growth, were not reached. Protein supply during 8–28 postnatal days was within the recommended range for both groups. These observations may explain the lack of growth difference in both time intervals. GA and birthweight SDS were negatively associated with protein supply during the first week, reflecting the higher nutrition volumes administrated in infants of lower GA and, or, SGA, according to the feeding protocols in Uppsala NICU. As expected, the duration of UAC in place was positively associated with the amount of protein supply during the first week.

Our findings are in agreement with previous studies showing no difference in weight gain in the first 28 postnatal days for high versus low amino acid administration in preterm infants.[18-20]

TABLE 5 Neonatal morbidities by type of UAC infusion in extremely low gestational age infants

	UAC with AA *n* = 41		UAC with normal saline/DW10 *n* = 30		
Variable	***N***	**%**	***N***	**%**	***p*-value**
BPD[d]					
No	6	15.0	5	17.9	.57[a]
Moderate	17	42.5	13	46.4	
Severe	17	42.5	10	35.7	
PDA ligation					
No	21	51.2	20	66.7	.19[b]
Yes	20	48.8	10	33.3	
NEC surgery					
No	40	97.6	28	93.3	.57[c]
Yes	1	2.4	2	6.7	
ROP[d]					
No	14	35.0	8	28.6	.21[a]
Moderate	15	37.5	7	25.0	
Severe	11	27.5	13	46.4	
IVH					
No	31	75.6	19	63.3	.22[a]
Moderate	7	17.1	6	20.0	
Severe	3	7.3	5	16.7	
Sepsis[e]					
No	32	78.0	25	83.3	.58[b]
Yes	9	22.0	5	16.7	
UAC-related thrombosis[e]					
No	40	97.6	30	100.0	1.00[c]
Yes	1	2.4	0	0.0	

Abbreviations: AA, amino acid solution; BPD, bronchopulmonary dysplasia; DW10, 10% dextrose in water; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, persistent ductus arteriosus; ROP, retinopathy of prematurity; UAC, umbilical artery catheter.

[a]*p*-value derived from Mann-Whitney *U* test.

[b]*p*-value derived from chi-square test.

[c]*p*-value derived from Fisher´s exact test.

[d]Available data for 68 infants, due to deaths before reaching the age for diagnosis.

[e]At least one verified sepsis episode/UAC–related thrombosis during the first two postnatal weeks.

Blanco et al found no difference in HC at birth and at discharge,[20] although another study described higher HC at 28 postnatal days and 36 weeks corrected GA, in favour of the group receiving more protein.[21] Vlaardingerbroek et al. did not find any difference in the mean linear growth rate between the groups during the first 28 postnatal days.[18] According to a meta-analysis, a combination of early and high-dose supplementation of AA in very low birthweight infants yielded no benefits on anthropometric outcomes when compared to later or lower-dose supplementation.[22]

The utilisation of the AA supply requires sufficient energy intake.[1] Guidelines published by ESPGHAN/ESPEN/ESPR/CSPEN working group in 2018 suggest that AA intake of 2.5–3.5 g/kg/day from postnatal day 2 onwards should be accompanied by non-protein intakes >65 kcal/kg/day.[1] In our study, the increase in protein supply was not accompanied by a proportional increase in total energy administration, providing a possible explanation for the lack of growth benefit. Alternatively, one could speculate that the difference in protein supply between the groups might not be large enough or that the exposure period of the first postnatal week was too short to cause a noticeable change in growth.

As shown previously,[7] the duration of antibiotics seemed to be related to lower weight gain during postnatal days 8–28, which indirectly reflects the growth restriction seen in infants with infection. Baseline SDS were negative predictors of the growth outcomes, in the time intervals investigated, as previously described.[7,23] It has been speculated that a growth-restricted neonate is more resistant to starvation-induced growth failure, which may be due to foetal metabolic programming, causing more effective energy retention.[7]

In line with previous results, AA infusion did not seem to affect the incidence of NEC, IVH, PDA ligation and sepsis,[11] further suggesting unaffected incidence of BPD, ROP and UAC-related thrombosis. Blanco et al. showed that early and high intravenous AA supplementation was not related to the incidence of IVH, periventricular leukomalacia, ROP, NEC, or the overall mortality,[20] and Clark et al. did not find differences in sepsis, PDA ligation, IVH, or NEC, between high versus low dose of AA supplementation.[19] A study comparing the administration of total parenteral nutrition through UAC with administration though central venous catheter found no significant difference in the rate of infection.[24] However, it should be noted that our study is not powered to draw safe conclusions on NEC.

This study included ELGANs treated in the same NICU, thus exposed to common neonatal care practices, making them more comparable. The before and after design of the study is more likely to indicate causal effects of AA infusion, due to the temporal sequence between exposure and outcomes. The study controls for various confounders and important proxies of severity of illness (duration of mechanical ventilation and antibiotics). Analyses were conducted separately for 0–7 and 8–28 postnatal days, in order to disentangle the potential effects of the transitional weight loss attributed to the postnatal contraction of extracellular water volume.[25] Furthermore, the availability of detailed nutritional data for the whole study period made it possible to make group comparisons for total fluid, energy and macronutrient intakes other than protein, which could interfere with infant growth.[7]

This study had several limitations. The one-day longer median UAC duration in the AA group compared to control group should be pointed out, although the difference was not statistically significant and the UAC duration was included as a covariate in multiple linear regression analyses. The relatively small number of participants increases the risk of type II error due to lack of power, especially when it comes to less frequent observations, such as NEC[26] and severe UAC-related complications.[10,12] Moreover, the frequency of UAC-related complications may be underestimated, as no diagnostic methods, such as serial ultrasound examinations were conducted proactively.[8] Besides, data on the number of blood draws or the reason of UAC removal were not available. The before and after nature of the study has the intrinsic risk of bias from cohort effects, due to changes in neonatal care over time. Nevertheless, there were no noteworthy changes in neonatal care at Uppsala NICU during the study period, apart from the one currently evaluated. Lastly, the study did not include a wash-out period after the new clinical practice was introduced. Nevertheless, the type of UAC infusion was clearly documented in the medical records.

5 | CONCLUSION

This study suggests that infusion of isotonic AA solution instead of normal saline/DW10 to maintain UAC patency in ELGANs is a safe clinical practice that may be associated with higher protein supply during the first postnatal week, although not associated with growth benefit during the first 28 postnatal days.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Gialamas S, Sjöström ES, Diderholm B, Domellöf M, Ahlsson F. Amino acid infusions in umbilical artery catheters enhance protein administration in infants born at extremely low gestational age. Acta Paediatr. 2022;111:536–545. doi:10.1111/apa.16196