Postnatal Head Growth in Preterm Infants: A Randomized Controlled Parenteral Nutrition Study

WHAT'S KNOWN ON THIS SUBJECT: Preterm infants dependent on parenteral nutrition are vulnerable to deficits in early postnatal nutritional intake. This coincides with a period of suboptimal head growth. Observational studies indicate that poor nutritional intake is associated with suboptimal head growth and neurodevelopmental outcome.

WHAT THIS STUDY ADDS: This study provides randomized controlled trial evidence that head growth failure in the first 4 weeks of life can be ameliorated with early nutritional intervention. Early macronutrient intake can be enhanced by optimizing a standardized, concentrated neonatal parenteral nutrition regimen.

abstract

BACKGROUND: Early postnatal head growth failure is well recognized in very preterm infants (VPIs). This coincides with the characteristic nutritional deficits that occur in these parenteral nutrition (PN) dependent infants in the first month of life. Head circumference (HC) is correlated with brain volume and later neurodevelopmental outcome. We hypothesized that a Standardized, Concentrated With Added Macronutrients Parenteral (SCAMP) nutrition regimen would improve early head growth. The aim was to compare the change in HC (ΔHC) and HC SD score (ΔSDS) achieved at day 28 in VPIs randomly assigned to receive SCAMP nutrition or a control standardized, concentrated PN regimen.

METHODS: Control PN (10% glucose, 2.8 g/kg per day protein/lipid) was started within 6 hours of birth. VPIs (birth weight <1200 g; gestation <29 weeks) were randomly assigned to either start SCAMP (12% glucose, 3.8 g/kg per day protein/lipid) or remain on the control regimen. HC was measured weekly. Actual daily nutritional intake data were collected for days 1 to 28.

RESULTS: There were no differences in demographic data between SCAMP (n = 74) and control (n = 76) groups. Comparing cumulative 28-day intakes, the SCAMP group received 11% more protein and 7% more energy. The SCAMP group had a greater ΔHC at 28 days ($P <$ .001). The difference between the means (95% confidence interval) for ΔHC was 5 mm (2 to 8), and ΔSDS was 0.37 (0.17 to 0.58). HC differences are still apparent at 36 weeks' corrected gestational age.

CONCLUSIONS: Early postnatal head growth failure in VPIs can be ameliorated by optimizing PN. *Pediatrics* 2014;133:e120–e128

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KEY WORDS

parenteral nutrition, preterm, head circumference, brain growth, protein, energy

ABBREVIATIONS

CGA—corrected gestational age
E/DBM—expressed or donor breast milk
HC—head circumference
ΔHC—change in head circumference
IGF-I—insulin-like growth factor-I
LWH—Liverpool Women's Hospital
NEC—necrotizing enterocolitis
PN—parenteral nutrition
RCT—randomized controlled trial
SCAMP—Standardized, Concentrated With Added Macronutrients Parenteral
SDS—standard deviation score
VPI—very preterm infant

Dr Morgan developed the original concept and designed the study, ensured regulatory approvals, performed some study measurements, data collection and collation, coordinated data analysis, and drafted the initial manuscript; Mr McGowan performed most of the study measurements, data collection, and collation, contributed to data analysis and made study design modifications; Mr Herwitker was involved with study design and regulatory approval, overseeing study PN manufacture, and some data collation; Ms Hart provided the medical statistical support at the design, monitoring, and analytical stages of the study; Dr Turner was involved in study design and data analysis; and all authors approved the final manuscript as submitted.

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Improved survival of very preterm infants (VPIs) has highlighted the importance of the associated long-term morbidities, especially impaired neurocognitive outcome. This group of infants is particularly vulnerable to postnatal growth failure. This coincides with the nutritional deficit that develops in VPIs in the first few weeks of life.[1,2] The deficit refers to the gap between the energy and protein actually provided and that required to mimic fetal growth rates. This postnatal growth failure was described in detail by Ehrenkranz,[3] who produced growth curves based on gestation and birth weight for infants <30 weeks' gestation. Growth in head circumference (HC) was also insufficient to match the fetal reference curves.[3] This insufficiency manifests as a growth curve falling away from the original centile and an falling SD score (SDS) in the early postnatal period. The nadir in head growth (based on lowest SDS) appears to be ~4 weeks postnatal age[4–6] for VPIs. Although there is usually a period of later catch-up head growth, the deficit persists after 36 weeks' corrected gestational age (CGA).[7] Head growth is an especially important measure of growth failure because it correlates with brain growth.[8] The correlation between HC and brain volume has also been shown by using neuroimaging at term.[9] Brain growth between birth and the expected date of delivery are key predictors of long-term brain growth.[10,11] Hack et al[12,13] showed that subnormal head size at 8 months was predictive of poorer verbal and performance IQ scores at 3[12] and 8[13] years.

VPIs have a gut that is too immature to digest milk in sufficient quantity to meet nutritional requirements. Virtually all preterm infants <29 weeks' gestation and <1200 g require parenteral nutrition (PN) for a period that depends on gestation birth weight and other morbidities. The mean duration of PN dependency in these infants is 15 days.[3,14] All aspects of contemporary neonatal PN regimens, from manufacture to administration, limit nutritional intakes in the PN-dependent period after birth. These restrictions prevent the delivery of sufficient nutrition to meet the recommended requirements for VPI.[1,2,5,15] Changing early nutritional policy can improve growth in large preterm cohorts[16] including discharge HC.[17] However, PN is a complex nutritional intervention that is difficult to investigate in randomized controlled trials (RCTs). No published[14,18] RCTs have achieved recommended[19] protein and energy intakes in VPIs in the first few weeks of life. No RCT has investigated the effect of nutritional interventions on early neonatal head growth.

We have developed a standardized, concentrated neonatal PN regimen that optimizes protein and energy intake in VPIs in the PN-dependent period. Concentrating PN ensures the combined volume of aqueous PN and intravenous lipid is much less than the total daily fluid intake. The difference is made up by a supplementary glucose infusion. When other intravenous infusions are administered concurrently, the supplementary infusion is reduced and maintains the intravenous amino acid (aqueous PN) and lipid intake. This regimen allows nutrient intake to be protected despite the characteristically complex fluid, electrolyte, and drug infusions required by VPIs. It has been shown to be effective in optimizing actual protein and energy intake in the PN-dependent period of VPIs.[5,20].

We modified our original standardized concentrated neonatal PN regimen (the control regimen) by increasing the macronutrient (protein, lipid, and glucose) content by ~30% and so created the Standardized, Concentrated With Added Macronutrients Parenteral (SCAMP) nutrition regimen.[21] We hypothesized that the SCAMP nutrition regimen would improve early head growth. Accordingly, the aim of the study was to compare the change in HC (ΔHC) and change in SDS (ΔSDS) achieved at day 28 in VPIs randomly assigned to receive SCAMP nutrition or the control regimen.

METHODS

The study received ethical and regulatory approval. Eligible infants were born <29 weeks' gestation, weighed <1200 g, and were admitted to the NICU at Liverpool Women's Hospital (LWH) within 48 hours of birth. Exclusion criteria were infants thought unlikely to survive, infants with major congenital or chromosomal abnormalities, infants known to have a parenchymal brain lesion on cranial ultrasound scan before 48 hours age, and infants without parental consent.

This was a single-center, parallel group, RCT with blinding of caregivers, parents, and outcome assessors. For patient safety reasons, pharmacists were not blinded to treatment allocation. The control group received the standardized, concentrated neonatal parenteral nutrition formulation used in current clinical practice, and the intervention group received a similar formulation containing additional macronutrients (SCAMP nutrition). Where feasible, randomization occurred before 72 hours of age but always within 120 hours. The statistical package Intercooled Stata 10 (Stata Corp, College Station, TX) was used to generate block randomization codes within strata defined by gestation at birth: 24 to 26 and 27 to 28 completed weeks. Once generated, the randomization codes were sealed in opaque serially numbered envelopes and given to the pharmacy to store in a secure place. After written parental consent, the pharmacy opened the next sequential envelope in the correct stratum and provided the allocated intervention. In the case of

multiple births, each infant was individually randomly assigned.

Study PN

The control PN formulation was constituted according to the LWH PN policy. The SCAMP formulation differed only in the macronutrient content (Table 1). All study infants received the control PN regimen as soon after birth as possible. After randomization, infants were either maintained on the control regimen or switched to the SCAMP nutrition regimen with the maximum macronutrient intake. The regimens are described in detail in the published protocol.[21] The estimated osmolality (150 mL/kg per day) in the SCAMP regimen is higher than the control regimen (Table 1). There were no differences in the micronutrients, vitamins, or electrolytes provided by the 2 regimens.

All infants received clinical care in accordance with LWH PN protocol. This included protocols for fluid management; introducing, increasing, and stopping enteral feeds; biochemical monitoring; insulin-treated hyperglycemia; and reduction in lipid infusion rates for hypertriglyceridemia. The study intervention continued until 28 completed days of life. PN was discontinued once enteral feeds exceeded 75% total. The transition from PN to enteral feeds is described in the published protocol[21] and involved the preferential use of expressed or donor breast milk (E/DBM), which remained unfortified until 150 mL/kg per day enteral feeds. If PN were subsequently required, then study PN was administered according to the original randomization until day 28 of life.

Data Collection

HC measurement was performed by using a standard occipital-frontal HC nonstretchable lasso tape measure (Child Growth Foundation, London, United Kingdom). Each infant was assigned his or her own tape measure[22] with 90% measurements determining primary outcome performed by PM (intraobserver coefficient of variation 1.3%). The remainder was performed by Dr Morgan. Measurement technique was harmonized by performing the first 30 measurements jointly, so minimizing interobserver variation.[22] HC was measured to the nearest millimeter and converted to SDS.[23] Detailed intravenous/enteral nutrition, fluid, and drug infusion data were captured from routine nursing charts. The amino acid, glucose, lipid, and energy intake was calculated from the published PN composition data.[21] The enteral intake of protein, carbohydrate, lipid, and energy was calculated from average values for E/DBM[24] and/or manufacturer's published values. Patient demographic, mortality, and morbidity data were collected from the electronic patient record. The former allowed calculation of the Clinical Risk Index for Babies.[25] Morbidity outcomes were obtained for 36 weeks' CGA survivors with additional 28-day survivor outcomes for morbidities related to PN complications. These data were reported regularly to the Data Monitoring Committee throughout the period of recruitment. This included individual case reviews for specific complications when requested.

TABLE 1 Comparison Between Control and SCAMP Macronutrient Content and PN Fluid Volumes in a Total Fluid Volume of 150 mL/kg Per Day

PN Component in a Total Fluid Volume of 150 mL/kg per day	Control	SCAMP
Maximum protein, g/kg per day	2.8	3.8
Maximum lipid, g/kg per day	2.8	3.8
Maximum glucose, g/kg per day	13.5	15.6
Total calorie intake, kcal/kg per day	85	108
Maximum aqueous PN volume, mL/kg per day	85	100
Maximum intravenous lipid volume, mL/kg per day	15	20
Maximum supplementary dextrose volume, mL/kg per day)	50	30
Estimated combined osmolality, mOsmol/L water	855	1025
Electrolyte provision, mmoL/kg per day	Control formulation	As for control
Vitamin and trace element provision	Control formulation	As for control

Statistical Methods

The primary analysis compared the ΔHC and ΔSDS achieved at day 28 in VPIs randomly assigned to receive SCAMP nutrition or the control regimen. The ΔHC (mm) and ΔSDS values for each infant were calculated as mean daily rates (for the study intervention period) and then multiplied by the mean duration of the intervention period for all infants (25 days).[21] This approach indicates a mean ΔHC of 32 mm for the intervention period, using standard preterm reference curves[23] and an estimated mean ΔHC of 21 mm in the control group by using previous head growth data.[5,14] The power calculation determined a sample size of 75 (assuming a survival rate of 80% of recruited infants) in each group had 80% power to detect a difference of 6 mm between the 2 groups for the mean ΔHC assuming a common SD of 12 mm[5,14] and analysis based on using a 2-group *t* test with a 0.05 2−sided significance level.[21]

Statistical Analysis

Data were analyzed by using Intercooled Stata 11, R2.15.1 (StataCorp, College Station, TX), and SPSS 20 (IBM SPSS Statistics, IBM Corporation). The primary outcome was analyzed with a general linear model controlling for stratum, checked by sensitivity analyses, in Stata. Sensitivity analyses comprised: including covariates to adjust for important group imbalances, identifying and removing potentially influential observations, taking account of multiple births, and joint modeling

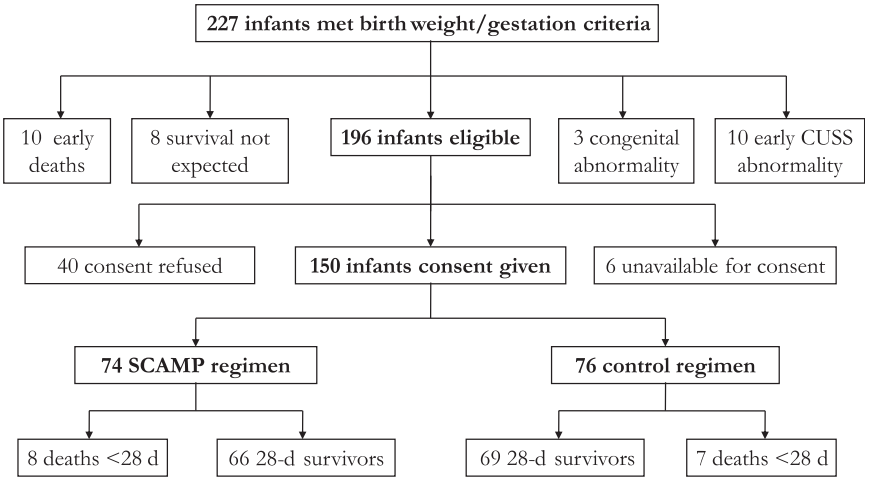

FIGURE 1
Schematic diagram summarizing outcomes of all eligible infants and numbers of survivors at 28 days. CUSS: Cranial ultrasound scan.

with survival data. Longitudinal joint modeling of HC and survival over 4 weeks was undertaken in R2.15.1 (routine JoineR), and Stata or SPSS generated summary statistics, 2-group *t* tests, χ^2 tests, and linear models as appropriate.

RESULTS

Infants were recruited at the LWH between October 2009 and July 2012. The pathway of recruitment and randomization is summarized in Fig 1. There were no study withdrawals (apart from deaths). The basic demographic data are summarized in Table 2. There were no clinically important differences between the SCAMP and control groups including factors relating to nutritional management before randomization.

Table 3 summarizes the weekly protein and energy intakes from birth. PN protein (intravenous amino acids) and energy is also described. Progressing from postnatal week 1 to 4, PN falls as a proportion of total nutrient intake. Week 1 nutrient intake data include protein and energy intake pre-randomization. During the 28-day intervention period, the SCAMP group received 11% more total protein and 7% more total energy intake. For protein and energy derived from PN, the mean percentages were 26% and 21%, respectively.

Table 4 summarizes the primary outcome data (day 28) and key secondary outcomes relating to head growth. It reveals a higher rate of head growth in the SCAMP group compared with control, with highly statistically significant differences by day 28. A model controlling for birth weight, gender, and clustering (due to multiple births in the sample) gave almost identical results. Longitudinal joint modeling of HC and survival confirmed a differential head growth rate over the study intervention period, consistent with the primary analysis (data not shown). The difference in primary outcome was higher in the lower gestation stratum, although this interaction effect was not statistically significant (ΔHC: 4.2 [−1.7 to 10.0]; $P = .16$ and ΔSDS: 0.28 [−0.14 to 0.71]; $P = .18$). The mean difference in ΔHC at 28 days equates to a 6% difference in estimated brain weight by using published mathematical formulas based

TABLE 2 Comparison Between SCAMP and Control Groups: Demographic Data and Nutritional Factors Pre-randomization

Demographic Factors	SCAMP, *n* = 74	Control, *n* = 76
Birth weight, mean (SD), g	900 (158)	884 (183)
Birth weight, mean (SD), SDS	−0.47 (0.79)	−0.47 (0.73)
Gestation, mean (SD), wk	26.8 (1.3)	26.6 (1.4)
Small for gestational age, *n* (%), SDS < −2	4 (5)	1 (1)
Gender, *n* (%), boy	44 (60)	39 (51)
Multiple birth, *n* (%)	26 (35)	29 (38)
Inborn, *n* (%)	64 (87)	60 (79)
Caesarean delivery, *n* (%)	32 (43)	34 (45)
Antenatal steroids, *n* (%), ≥1 dose	70 (95)	73 (96)
Surfactant, *n* (%), ≥1 dose	73 (99)	76 (100)
CPR required at delivery, *n* (%)	6 (8)	4 (5)
Worst lactate < 12 h, mean (SD), mmol/L	5.3 (4.2)	4.9 (3.7)
Worst base deficit < 12 h, mean (SD), mmol/L	−6.8 (5.4)	−6.6 (5.2)
Clinical Risk Index for Babies score, mean (SD)	10.8 (2.3)	10.9 (2.4)
Nutritional factors		
Age PN started, median (IQR), h	3 (2–6)	3 (2–8)
Total protein intake, mean (SD), g/kg	5.4 (2.9)	5.6 (2.9)
PN protein intake, mean (SD), g/kg	5.3 (2.8)	5.5 (2.8)
Total calorie intake, mean (SD), kcal/kg	146 (79)	152 (81)
Age study PN started, median (IQR), h	70 (46–94)	67 (47–93)
Weight at randomization, mean (SD), SDS	−0.90 (0.73)	−0.91 (0.64)

CPR, cardiopulmonary resuscitation; IQR, interquartile range.

TABLE 3 Comparison Between SCAMP and Control Groups (28-Day Survivors)

	Protein Intake (g/kg per day)			Calorie Intake (kcal/kg per day)		
	SCAMP, *n* = 66	Control, *n* = 69	Difference (95% CI)	SCAMP, *n* = 66	Control, *n* = 69	Difference (95% CI)
Week 1						
Total	2.8 (0.3)	2.4 (0.3)	0.4 (0.3 to 0.5)	74 (7)	68 (6)	6 (4 to 8)
Parenteral	2.7 (0.3)	2.2 (1.5)	0.4 (0.3 to 0.5)	70 (8)	63 (6)	6 (4 to 8)
Week 2						
Total	3.6 (0.5)	3.0 (0.2)	0.6 (0.5 to 0.8)	109 (10)	95 (9)	14 (11 to 17)
Parenteral	3.0 (0.9)	2.3 (0.6)	0.7 (0.4 to 1.0)	82 (23)	65 (19)	17 (10 to 14)
Week 3						
Total	3.1 (0.6)	3.0 (0.5)	0.2 (0 to 0.4)	110 (15)	105 (9)	5 (0 to 10)
Parenteral	1.4 (1.3)	1.1 (1.1)	0.3 (−0.1 to 0.7)	40 (36)	31 (31)	9 (−2 to 21)
Week 4						
Total	3.2 (0.6)	3.2 (0.7)	0.1 (−0.2 to 0.3)	115 (17)	113 (23)	2 (−5 to 9)
Parenteral	0.8 (1.3)	0.6 (0.9)	0.2 (−0.2 to 0.6)	23 (34)	18 (26)	5 (−5 to 16)
Cumulative (Total: day 1–28)	Protein intake (g/kg per 28 d)			Calorie intake (kcal/kg per 28 d)		
Total	89.4 (8.2)	80.7 (8.0)	8.7 (6.0 to 11.5)	2851 (251)	2664 (307)	188 (92 to 283)
Parenteral	54.8 (20.2)	43.6 (15.7)	11.2 (5.0 to 17.3)	1500 (555)	1237 (461)	263 (89 to 436)

CI, confidence interval. Mean (SD) daily protein and energy intake for each of the first 4 weeks of life; cumulative mean (SD) daily protein and energy intake for whole study period.

on postmortem data.[7] This rises to 10% for the more immature infant stratum. Table 4 also summarizes mean HC and SDS data. This indicates the difference in HC is still statistically significant at 36 weeks' CGA despite clinically important catch-up head growth in both groups after 28 days postnatal age. This suggests a 5% difference in brain weight at 36 weeks' CGA.[8]

Virtually all infants had an HC SDS less than zero at randomization (reflecting poor antenatal growth). Scatter plots were used to investigate whether HC SDS at randomization might have influenced early postnatal head growth. ΔHC at 28 days was only weakly correlated with HC SDS at randomization in this study sample ($r = -0.2$ in each group). The relationship between total protein and energy intakes and the primary outcome was also explored. Exploratory regression analyses suggested a positive association between protein intake and primary outcome (protein $r = 0.4$; total calorie $r = 0.1$). The nonprotein calorie:protein ratio was also associated with the primary outcome ($r = -0.4$), and this ratio and total protein intake were both significant in the multiple regression analysis.

Table 5 summarizes the key secondary outcomes relating to weight over the 28-day intervention period and at 36 weeks' CGA. Table 6 summarizes mortality and preterm complications at the end of the 28-day intervention period and at 36 weeks' CGA. No statistically significant differences in mortality or major preterm complications were identified. However, the possibility that major cranial ultrasound scan abnormalities could affect the primary outcome measure was considered. Additional sensitivity analyses demonstrated that our estimate of treatment effect was not affected by the presence of grade 3 or 4 intraventricular hemorrhage, all major cranial ultrasound scan abnormalities combined, or necrotizing enterocolitis (NEC).

DISCUSSION

This study reveals that head growth in the first 28 days of life can be improved

TABLE 4 Comparison Between SCAMP and Control Groups

Age	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)
Measurement		ΔHC (mm)			ΔSDS	
Day 28	31 (9)	26 (9)	5 (2 to 8) *P* < .001	+0.05 (0.66)	−0.32 (0.65)	0.37 (0.17 to 0.58) *P* = .001
Measurement		HC (mm)			SDS	
Randomization	240 (12)	240 (13)	—	−1.55 (0.70)	−1.48 (0.67)	—
Day 7	244 (12)	243 (14)	—	−1.64 (0.69)	−1.66 (0.69)	—
Day 14	252 (12)	250 (14)	—	−1.68 (0.63)	−1.78 (0.72)	—
Day 21	261 (14)	257 (16)	—	−1.67 (0.70)	−1.89 (0.75)	—
Day 28	271 (16)	265 (17)	6 (2 to 10) *P* = .007	−1.51 (0.87)	−1.81 (0.86)	0.30 (0.01 to 0.60) *P* = .042
36 weeks' CGA	316 (13) *n* = 63	311 (15) *n* = 63	5 (0.1 to 10) *P* = .046	−0.93 (1.06) *n* = 63	−1.32 (1.18) *n* = 63	0.40 (0.005 to 0.79) *P* = .047

CI, confidence interval. Mean (SD) ΔHC and ΔSDS between randomization and day 28 (28-d survivors); mean (SD) HC and SDS at randomization, 7, 14, 21, and 28 d (28-d survivors) and 36 weeks' CGA (survivors). *P* value controlling for stratum. *P* values are provided only for the primary outcome measure and major secondary outcomes.

TABLE 5 Comparison Between SCAMP and Control Groups

Age	Weight, g			SDS		
	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)
Randomization	909 (154)	898 (172)	—	−0.86 (0.70)	−0.88 (0.64)	—
Day 7	934 (123)	903 (153)	—	−0.92 (0.59)	−1.02 (0.59)	—
Day 14	1044 (152)	989 (171)	—	−0.90 (0.62)	−1.10 (0.58)	—
Day 21	1147 (173)	1072 (209)	—	−0.99 (0.60)	−1.24 (0.65)	—
Day 28	1269 (222)	1212 (242)	61 (−10 to 132) *P* = .09	−1.05 (0.71)	−1.19 (0.75)	0.14 (−0.11 to 0.38) *P* = .28
36 weeks' CGA	2082 (293) *n* = 62	1976 (346) *n* = 62	106 (−9 to 221) *P* = .07	−1.41 (0.72) *n* = 62	−1.68 (0.88) *n* = 62	0.26 (−0.03 to 0.55) *P* = .07

Mean (SD) weight and SDS at randomization, 7, 14, 21, and 28 d (28-d survivors) and 36 weeks' CGA (survivors). *P* value controlling for stratum. *P* values are only provided for major secondary outcomes.

TABLE 6 Comparison Between SCAMP and Control Groups: Major Preterm Complications in 28-Day Survivors and Survivors to 36 Weeks' CGA

	SCAMP, *n* = 74	Control, *n* = 76	*P*
28-d Outcomes			
Mortality	8 (11%)	7 (9%)	.74
28-d survivors	*n* = 66	*n* = 69	
PDA (requiring medical treatment or surgical ligation)	24 (36)	28 (41)	.61
NEC (requiring surgical intervention)	5 (8)	9 (13)	.30
Late onset sepsis (>72 h) (1 or more positive blood/CSF cultures)	21 (32)	29 (42)	.28
Acute renal failure (≥2 d with serum creatinine > 100 mmol/L)	13 (20)	8 (12)	.19
Conjugated hyperbilirubinemia (conjugated bilirubin > 50 mmol/L)	6 (9)	8 (12)	.63
36 weeks' CGA outcomes			
Mortality	11 (15)	12 (16)	.88
36 weeks' CGA survivors	*n* = 63	*n* = 64	
PDA	25 (40)	25 (39)	.94
NEC	5 (8)	9 (14)	.27
Late onset sepsis (>72 h)	26 (41)	28 (44)	.86
Conjugated hyperbilirubinemia	13 (21)	12 (19)	.89
All major cranial ultrasound scan abnormalities	11 (18)	5 (8)	.10
Grade 3/4 intraventricular hemorrhage	5 (8)	2 (3)	.27
PVL	4 (6)	2 (3)	.44
Bronchopulmonary dysplasia (oxygen dependency at 36 weeks' CGA)	42 (67)	42 (66)	.90
Retinopathy of prematurity (requiring laser treatment)	8 (13)	3 (5)	.11

CSF, cerebrospinal fluid; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia. Data shown as number (%) of infants.

by increasing PN protein and energy intake in infants < 29 weeks' gestation. The effect persists until 36 weeks' CGA. Both the SCAMP and control groups achieved higher mean ΔHC than anticipated, with the former (31 mm) approaching that expected from the reference population growth curve (32 mm). The control group still revealed the characteristic fall in SDS described in previous work, with a nadir at 3 to 4 weeks' postnatal age.[4,5] These findings provide the first RCT evidence that early head growth failure can be ameliorated by early nutritional intervention in VPIs. Using a published mathematical formula for HC and brain weight, the estimated difference between the groups would be 6% at 28 days and 5% at 36 weeks' CGA.[8] The estimates are consistent with those using alternative formulae.[26,27] These data are also consistent with the data relating HC and brain volume by using MRI.[8] Thus, a range of methods yields concordant estimates for the effect on brain growth expected of the study intervention. In a small number of infants, the observed growth may not represent optimal head growth because problems such as posthemorrhagic ventricular dilatation can also increase HC. The sensitivity analyses indicate that this is not a likely explanation of these findings.

In humans, maximum brain growth acceleration occurs at 24 to 25 weeks' gestation[27] heralding the onset of the brain growth spurt that takes place during the last trimester and the first 3 months of postnatal life.[27,28] High growth rates persist until the end of the second year.[28] Malnutrition during this critical period of central nervous system development may cause irreversible long-term neurologic deficits.[28] There are clinical trials that support a role for nutritional intervention during this critical period to optimize cognitive development[29] and neurologic repair.[30] Our study was designed to focus on the first 28 days in preterm infants < 29 weeks' gestation because of the large nutritional deficits and head growth failure reported in this population. This period corresponds to the first part of the brain growth spurt in humans and may be particularly vulnerable to a nutritional insult even if later catch-up growth occurs. Our study findings indicate that preventing head growth failure in the first 28 days of life has a lasting impact on HC at 36 weeks'

CGA even though catch-up growth took place in both groups. This may indicate there is a time limited opportunity to optimize head growth in the immediate postnatal period. The difference in head growth at 36 weeks' CGA has particular significance given the relationship between discharge HC and neurodevelopmental outcome.[10,11] Following Hack's original work[12,13] associating HC at 8 months with later IQ, more recent preterm cohorts have reproduced similar findings correlating head growth from birth to discharge with improved neurodevelopmental outcomes at 2 years[9,31,32] and 4 to 6 years.[32–35] A similar relationship between HC at 9 months and later cognitive function has also been described in term infant populations.[36] These observational studies consistently demonstrate the relationship between head growth in infancy and later neurodevelopment and suggest that the head growth in the period immediately after birth is a useful surrogate for important long-term outcomes.

This study reveals the effectiveness of the SCAMP nutrition regimen in optimizing PN protein and energy intake. Early protein intake appears particularly important in growth[37,38] and neurodevelopment.[39] This is consistent with our own study findings that suggest early protein intake is more influential on early head growth than calorie intake. Standardizing and concentrating neonatal PN is particularly effective at optimizing early protein intake.[20] Previous RCTs[14,18] investigating early neonatal PN failed to achieve optimal nutritional intakes. This may explain why the improved neurodevelopmental outcomes seen in large cohort studies[37] were not reproduced.[40] The principles of standardization and concentration have recently been applied by other workers to neonatal PN in observational studies and been similarly effective in optimizing nutritional intake.[41,42]

We were struck by the very low SDS for HC at randomization. The subsequent catch-up growth is well described in preterm infants.[43] There is consistent evidence that small for gestational age VPIs are at the greatest risk of future neurodevelopmental problems and that this reduces as the degree of catch-up head growth increases.[34,43] The SCAMP regimen allowed catch-up growth to start from a higher baseline. It has been suggested that postnatal growth failure (particularly HC) in VPIs is resistant to nutritional intervention during the first 4 postnatal weeks.[4] It has been hypothesized that this results from VPIs having somatotrophic axis immaturity: low insulin-like growth factor-I (IGF-I) levels are a consistent feature of this period.[4] IGF-I levels correlate with postnatal head and brain growth in VPIs.[44,45] IGF-I is also modulated by nutritional intake.[46] Our study clearly reveals that the pervasive failure to achieve adequate head growth should be attributed to inadequate nutrition.

Complex nutritional interventions are difficult to implement consistently in clinical practice and this creates challenges for study design. Our study specifically focused on the period of maximal PN delivery and was not designed to assess differences in PN before day 3. Our protocol ensured early introduction of amino acids (1.8 g/kg per day) in both groups, but we considered using >3 g/kg per day from birth in the SCAMP group a separate study question. Similarly, there was a fall in protein intake during the transition phase between PN and enteral feeding with unfortified E/DBM suggesting separate enteral feeding study is required. Our study design allowed parents >24 hours to consider the information. This design enhanced HC measurement accuracy by using 2 investigators and avoiding swelling/bruising and head molding often present at birth. However, the differing randomization times necessitated standardization of ΔHC findings. A potential weakness in study design was nonblinding of the pharmacy team. However, this is unlikely to have affected clinical care given complete blinding to treatment intervention at the cotside. The study was not powered to assess major preterm complications although detailed case analysis formed part of the study monitoring process. This did not suggest an atypical pattern of complications in either group. The SCAMP nutrition study is due to report neurodevelopmental outcomes at 2 to 3 years,[21] although it is not powered to detect a difference in this secondary outcome. Our findings provide the essential evidence required to develop a larger multicenter RCT powered to investigate early nutritional intervention and later neurodevelopment.

CONCLUSIONS

Postnatal head growth failure in the first 28 days of life can be ameliorated by optimizing PN protein and calorie intake in preterm infants <29 weeks' gestation. The effect persists until 36 weeks' CGA after the catch-up phase of head growth. Standardized, concentrated neonatal PN is an effective way of delivering early nutrition to VPIs.

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