Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial

Sabita Uthaya,[1,2*] Xinxue Liu,[3] Daphne Babalis,[3,4] Caroline Dore,[5] Jane Warwick,[3] Jimmy Bell,[6] Louise Thomas,[6] Deborah Ashby,[2] Giuliana Durighel,[6] Ash Ederies,[7] Monica Yanez-Lopez[4] and Neena Modi[1,2]

[1]Chelsea and Westminster NHS Foundation Trust, London, UK
[2]Department of Medicine, Section of Infectious Diseases, Imperial College London, London, UK
[3]Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK
[4]Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK
[5]University College London Comprehensive Clinical Trials Unit, University College London, London, UK
[6]Metabolic and Molecular Imaging Research Group, Medical Research Council Clinical Science Centre, Imperial College London, London, UK
[7]Institute of Clinical Sciences, Imperial College London and Medical Research Council Clinical Sciences Centre, Hammersmith Hospital, London, UK

*Corresponding author

Declared competing interests of authors: Sabita Uthaya is currently in the process of applying for a patent for the trial parenteral nutrition formulations. Jane Warwick has had personal fees paid for consultancy work by Novo Nordisk (Bagsværd, Denmark).

Published March 2016
DOI: 10.3310/eme03020

Scientific summary

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Efficacy and Mechanism Evaluation 2016; Vol. 3: No. 2
DOI: 10.3310/eme03020

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Delivering nutrition to very immature babies is challenging. Parenteral nutrition (PN) requires reliable intravenous access, pharmacist support and clinical expertise in minimising and treating complications. Gastrointestinal immaturity precludes early administration of milk volumes sufficient to support growth. In practice, PN and milk feeds are commenced at variable intervals after birth, with nutrient delivery increased incrementally. As a consequence, cumulative nutrient deficits are common and, by term, the majority of very preterm infants are lighter and shorter than healthy term-born counterparts. Although optimal postnatal growth velocity is uncertain, the association between slower growth and greater likelihood of neurodevelopmental impairment and cerebral palsy has provided justification for early PN provision. High amino acid intakes have been advocated, with the recommended daily intake (RDI) calculated on the basis of redressing cumulative deficits as well as matching intrauterine growth velocity. Intravenous lipid preparations containing fish oils have been recommended on the basis of clinical observations suggesting that they may be protective against hepatic dysfunction, a frequent concomitant of PN.

A diet with a low protein-to-energy ratio results in lower lean body mass and greater adiposity. Thus, in the short term, weight gain, though a widely used outcome measure, may not be as revealing as body composition. Monitoring lipid tolerance is problematic, as normative ranges for circulating lipids remain inadequately defined in very preterm babies and relationships to long-term outcomes are unclear. Whole-body magnetic resonance imaging (MRI) can be employed to assess body composition directly and in vivo magnetic resonance spectroscopy (MRS) to non-invasively assess hepatic lipid; the latter compares favourably with the gold standard, liver biopsy, for the quantitative assessment of hepatic steatosis.

We designed a clinical trial to test the hypotheses that the immediate delivery of the RDI of parenteral amino acids compared with incremental provision is more efficacious in increasing lean (non-adipose) body mass at term, and a mechanism of action of 20% soya bean oil, medium-chain triglycerides, olive oil, fish oil lipid (SMOFlipid®; Fresenius Kabi AG, Richmond Hill, ON, Canada) compared with 20% Intralipid® (Fresenius Kabi AG, Richmond Hill, ON, Canada) is to reduce intrahepatocellular lipid (IHCL) content.

Objectives

Amino acid intervention

To evaluate whether or not immediate rather than incremental introduction of the RDI of amino acids (Imm-RDI) in extremely preterm infants results in:

- greater accrual of non-adipose (lean) body mass at term (primary objective)
- increased brain volume at term (secondary objective)
- reduced insulin resistance at term (secondary objective)
- reduced ratio of internal to subcutaneous adipose tissue (AT) at term (secondary objective)
- a lower drop in weight standard deviation (SD) score between birth and term equivalent (secondary objective).

Lipid intervention

To evaluate whether or not 20% SMOFlipid (with a lower ratio of *n*-6 to *n*-3 fatty acids) compared with 20% Intralipid in extremely preterm infants results in:

- reduced IHCL content at term age equivalent (primary objective)
- reduced incidence of hypertriglyceridaemia and hyperbilirubinaemia (secondary objective).

Methods

Trial design

This was a multicentre, randomised, 2 × 2 factorial and double-blind controlled trial in four UK centres, in London and south-east England. Eligible preterm infants were randomised, within 24 hours of birth, to receive (1) either incremental amino acids (Inc-AA) in PN or the RDI of amino acids (Imm-RDI) from day 1; and (2) either 20% Intralipid or 20% SMOFlipid.

There were four randomised groups:

1. Inc-AA and 20% Intralipid (Inc-AA/Intralipid)
2. Inc-AA and 20% SMOFlipid (Inc-AA/SMOFlipid)
3. Imm-AA and 20% Intralipid (Imm-RDI/Intralipid)
4. Imm-AA and 20% SMOFlipid (Imm-RDI/SMOFlipid).

Participants

Preterm infants (born before 31 weeks of gestation) requiring nutritional support in the form of PN.

Inclusion criteria

- Preterm infants born before 31 weeks of gestation (defined as ≤ 30 weeks and 6 days).
- Written informed consent from parents.

Exclusion criteria

- Major congenital or life-threatening abnormalities.
- Inability to randomise in time to allow administration of trial PN within 24 hours of birth.

Interventions

There were two interventions: (1) the amount of amino acids in PN and (2) the type of lipid formulation. All other components of PN were consistent across the four treatment groups. The intervention was commenced within 24 hours of birth. Nutritional intake, both parenteral and enteral, was guided by prespecified protocols that were provided in an investigator's manual. In the control arm of amino acid intake, infants received 1.7 g/kg/day amino acids on day 1 of postnatal life. This increased to 2.1 g/kg/day on day 2 and a maximum of 2.7 g/kg/day from day 3. In the intervention group, infants received 3.6 g/kg/day from day 1. On days 1 and 2, PN was provided in an aqueous form at a concentration of 90 ml/kg/day increasing to 120 ml/kg/day from day 3 onwards. Carbohydrate intake was 8.6 g/kg/day from day 1. Lipid intake was 2 g/kg/day on day 1 increasing to 3 g/kg/day from day 2 onwards. Infants were also randomised to receive lipid as either 20% Intralipid or 20% SMOFlipid. Day 1 was defined as the duration between birth and when the first bag of PN was changed. Bag changes occurred daily at 17.00. PN was dispensed only between 09.00 and 17.00. The duration of day 1 was variable and dependent on infant time of birth. Subsequently, all infants received the intended volumes as described above.

The interventions ceased once the infant was established on milk feeds of 150 ml/kg/day for at least 24 hours. If the infant was subsequently placed nil by mouth after this point, PN was prescribed in accordance with local practice as determined by the supervising clinician.

Outcomes

Primary outcomes

Efficacy of the early introduction of the RDI of amino acids was assessed by whole-body MRI to measure non-adipose or lean mass. The efficacy of lipid composition was assessed by MRS to measure IHCL content. These assessments were done at term age equivalent, between 37 and 44 weeks postmenstrual age.

Measurement of lean body mass

Lean body mass was calculated by subtracting AT mass from the weight of the baby on the day of the scan.

Measurement of intrahepatocellular lipid content

Efficacy of SMOFlipid was assessed by liver MRS to measure IHCL content. This was done at term age equivalent, between 37 and 44 weeks postmenstrual age.

Secondary outcomes

- Quantity and distribution of AT.
- Total and regional brain volumes.
- Metabolic index of insulin sensitivity [as measured by the quantitative insulin sensitivity check index (QUICKI)].
- Serum lipids and bilirubin.
- Incidence of death.
- Anthropometry.

Sample size and statistical analysis

The sample size was based on the estimate that 64 infants in each pairwise group (Imm-RDI vs. Inc-AA) would provide 80% power (two-sided; 5% significance) to detect a 200-g difference in non-adipose mass assuming a SD of 400 g. This represents half the difference in non-adipose mass identified between very preterm and term-born infants in a prior experimental cohort. We have previously reported IHCL values for very preterm babies at term [mean lipid-to-water ratio 1.75 (SD 1.85), range 0.14–7.72]. As the distribution is positively skewed, a $\log_e$-transformation was used to provide IHCL mean lipid-to-water ratio [0.121 (SD 1.052); range –1.97 to 2.04]. It was calculated that 64 infants in each pairwise group would provide 80% power (5% significance) to detect a difference in mean IHCL values of 0.53 on the logarithmic scale. Back-transforming to the original scale of measurement, this is equivalent to a 40% decrease in IHCL content in the intervention group. It was assumed there would be no interaction between the interventions. Allowing for a 10% mortality and up to 10% dropout (including babies still in hospital at 44 weeks postmenstrual age), the aim was to recruit 160 infants or until 64 infants in each pairwise group completed primary outcome evaluations.

A modified intention-to-treat analysis was used, as it was anticipated that it would not be possible to obtain primary outcome measures in all infants. For the amino acid and lipid interventions, a multiple regression was used with non-adipose mass (g) or IHCL content (natural logarithmic scale) as the dependent variable and amino acid group (Inc-AA or Imm-RDI), lipid group (Intralipid or SMOFlipid), stratifying variables (gestational age, birthweight and centre), sex and age at assessment as the independent variables. An interaction term was added to assess if the effect of amino acid regimen is influenced by lipid type. In a planned secondary analysis, illness severity and nutritional intake was incorporated in the regression models to investigate their role as potential effect modifiers. All analyses were performed using Stata 13 (StataCorp LP, College Station, TX, USA).

Results

Of the 437 infants born before 31 weeks of gestation, 168 infants were randomised. A total of 133 infants were available for assessment of the primary outcome measures. Baseline characteristics of sex, gestational age at birth, anthropometry, maternal demographics, mode of delivery, antenatal steroid use, blood pressure on admission and time to commencing PN were similar across the four groups.

The median time to achieve a milk intake of 150 ml/kg/day for 24 hours for all infants randomised was similar across the four groups {Inc-AA/Intralipid: 12 days [interquartile range (IQR) 9–17.5 days]; Inc-RDI/SMOFlipid: 11.5 days [IQR 9–16 days]; Imm-RDI: 11 days [IQR 10–14 days]; and Imm-RDI/SMOFlipid: 13 days [IQR 9.5–18 days]}. The median length of hospital stay for all infants randomised was similar across the four groups [Inc-AA/Intralipid: 69.5 days (IQR 52–95 days); Inc-RDI/SMOFlipid: 61 days (IQR 45–88 days); Imm-RDI: 63 days (IQR 45–95 days); and Imm-RDI/SMOFlipid: 66.5 days (IQR 44–98 days)].

Nutritional intake from trial PN during the first week was similar across the four groups, except in the intake of protein. For ease of comparison between enteral and parenteral intakes, we express parenteral amino acid intake as protein (1 g of amino acids ≡ 0.89 g of protein). Trial PN protein intake was higher in the Imm-RDI arms, and carbohydrate and lipid intakes were similar across the four groups.

In relation to primary outcome measures, there were no significant differences in the quantity of non-AT mass between the groups randomised to Inc-AA and those randomised to the Imm-RDI {adjusted mean difference Imm-RDI, 1 g [95% confidence interval (CI) –108 to 111 g]; $p = 0.98$}. For the lipid composition intervention, there was no significant difference in IHCL content between the groups randomised to receive 20% Intralipid than for 20% SMOFlipid (adjusted mean ratio of lipid to water 1.1, 95% CI 0.8 to 1.6; $p = 0.58$).

There were no significant differences between the groups in the proportion of infants with abnormal biochemical indices namely serum glucose, worst base deficit in the previous 24 hours, total serum bilirubin, conjugated bilirubin, serum cholesterol, serum triglycerides, serum sodium, serum potassium, serum phosphate, serum calcium, serum creatinine, and alanine transaminase. However, Imm-RDI infants were more likely than Inc-AA infants to have blood urea nitrogen levels > 7 mmol/l [75% vs. 49% ($p < 0.01$)] and and > 10 mmol/l [49% vs. 18% ($p < 0.01$)]. Head circumference at term was smaller in the Imm-RDI group (mean difference –0.8 cm, 95% CI –1.5 to –0.1 cm; $p = 0.02$).

There were no significant differences, at term age equivalent, in secondary outcome measures of the quantity and distribution of AT, measure of insulin sensitivity (QUICKI), total cerebral volume, whole-brain volume, weight and length.

Conclusions

We conclude that commencement within 24 hours of birth of an Inc-AA regimen providing a maximum of 2.7 g/kg/day together with the early introduction of milk feeds, compared with the immediate provision of an amino acid intake of 3.6 g/kg/day, does not appear to be detrimental to body composition and may be safer. In addition, SMOFlipid does not reduce IHCL accumulation.

Extremely preterm infants at term age equivalent, with the early provision of PN according to a standardised regimen, can achieve the body composition nearer that of healthy term-born infants.

Before either of the interventions studied in this trial can be recommended as routine practice, long-term follow-up of functional outcomes of neurodevelopment as well as long-term body composition and metabolic health of both the trial interventions is essential.

The results do not support the calls for more aggressive nutrition in the extremely preterm infant nor the routine use of SMOFlipid as reflected in international consensus statements (higher amounts of amino acids) or as is increasingly seen in current practice.

A key ancillary observation of this trial is that the use of standard PN regimens is feasible, is acceptable to clinicians, even when blinded, can deliver desired nutritional intake without manipulation and is safe. In our opinion, standardised regimens that have been tested in the context of a randomised controlled trial should be adopted in routine clinical practice to reduce the clinical risk to infants from variation in practice.

We suggest that high amounts of amino acids be used only in the context of randomised clinical trials. Optimal amino acid intakes and intravenous lipid formulations for extremely preterm infants remain to be established.

Trial registration

This trial is registered as ISRCTN29665319 and EudraCT 2009–016731–34.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/99/04. The contractual start date was in February 2010. The final report began editorial review in January 2015 and was accepted for publication in October 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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