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Standardising neonatal parenteral nutrition: a suggested approach

Despite efforts to standardise parenteral nutrition (PN) in the past, different regimens exist owing to lack of consensus in the face of a deficit of evidence from high quality randomised clinical trials. In this article an approach to standardisation is presented based on the NEON trial, the largest clinical trial of PN in preterm infants to date. The trial demonstrated, in addition to its primary objectives, that standardised formulations are acceptable to clinicians, safe, stable and improve the nutritional intake in preterm infants especially in the early postnatal period.

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Key points

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1. Most preterm infants who receive PN do so during the period that enteral feeds are being introduced as a gradual transition from total PN to partial PN and on to full enteral feeds.
2. When considering macronutrient quantities in PN consideration must be given to enteral intakes.
3. Aiming to provide so-called 'recommended intakes' of all macronutrients in PN in the first week after birth is problematic.
4. When using standard PN formulations clinicians should use regimens that have been tested in high quality clinical trials with accompanying safety and efficacy data.

The case for standardisation

Two national reports in the UK have identified the variability in the prescribing, compounding and delivery of neonatal parenteral nutrition (PN) as a significant clinical risk, identifying the 'need for consistency in prescribing, dispensing, delivering and documenting parenteral nutrition use'.[1,2]

There are several international consensus guidelines and frameworks published for PN, however, the evidence-base underpinning current clinical practice is extremely poor. Working groups such as those of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) acknowledge the limited evidence base for current guidelines.[3] In particular, current approaches have not have been tested in randomised controlled trials (RCTs). The British Association of Perinatal Medicine framework[4] also recognised this, stating: "We note a need for clinicians, dietitians and pharmacists to keep abreast of new scientific evidence, and whenever possible to use PN regimens that have been tested in the context of a randomised clinical trial with relevant safety data considered".[5]

In the UK there have been two RCTs of efficacy of PN, the most recent of which is the NEON (nutritional evaluation and optimisation in neonates) trial.[6] The aim of this two-by-two factorial, double-blind multicentre RCT was to compare the effect of high (immediate recommended daily intake: Imm-RDI) versus low (incremental introduction: Inc-AA) parenteral amino acid delivery, commenced within 24 hours of birth, on body composition, and a multi-component lipid emulsion containing 30% soy bean oil, 30% medium chain triglycerides, 25% olive oil and 15% fish oil (SMOF) versus soy bean oil-based lipid emulsion (SO) on intra-hepato-cellular lipid (IHCL) content.

The second trial is the SCAMP (standardised concentrated additional macronutrients parenteral nutrition) trial.[7] The aim of this single-centre, unblinded study was to compare two different PN regimens, one with higher amounts of all three macronutrients, on head growth velocity.

The vast majority of preterm infants who receive PN do so during the period that enteral feeds are being introduced as a gradual transition from a brief period of total PN to partial PN and on to full enteral feeds. The median time to full enteral feeds in infants born at less than 31 weeks' gestation in the NEON trial was 11-12 days.[6,8] Data obtained from the National Data Analysis Unit (NDAU) in the course of progressing the National Neonatal PN Quality, Innovation, Productivity and Prevention (QIPP) in the London Operational Delivery Network (ODN) shows that in the two-year period, 2014 and 2015, in units in the London ODN, there were 1,798 babies born at less than 31 weeks' gestation who received PN before full enteral feeds were established.[9] Of these, two-thirds (1,198 babies, 66.6%) were no longer on PN by day 14 (**FIGURE 1**).

The median duration of PN in infants

born less than 31 weeks' gestation before full enteral feeds were established was consistent with that reported in the NEON trial (**FIGURE 2**). Of note is that there was wide variation in the number of babies still on PN at 14 days depending on unit of care, irrespective of level of care provided.

When considering macronutrient quantities in PN, consideration must be given to enteral intakes. Aiming to provide so-called 'recommended intakes' of all macronutrients in the first week after birth is nigh on impossible and leads to metabolic derangements that have the unintended consequence of reducing the volume of PN, hence not meeting the nutritional needs of the infant. In the minority of preterm infants who are still nil by mouth or on minimal milk feeds with no prospect of increasing enteral intakes after two weeks of postnatal age, consideration may be given to individualising PN as babies by this stage are likely to be more metabolically stable and able to tolerate higher intakes of macronutrients.

PN should be considered primarily as a vehicle for transport of macro and micronutrients, not electrolytes that can easily be administered in fluids or indeed orally, outside of PN. The NEON trial of 168 babies demonstrated effectively that standardising PN is feasible and acceptable to clinicians; only ten babies had aqueous trial PN stopped by the clinician, all transiently, for biochemical reasons (**TABLE 1**). The trial had standard protocols for dealing with biochemical abnormalities and demonstrated that it is possible to use a standard solution without the need for daily manipulations to the contents. The published report and paper contain the summary results of daily biochemistry of all patients recorded while on PN. NEON is the largest trial of preterm PN and the only double-blinded trial of its kind with detailed safety data published.

Despite efforts to standardise PN in the past in various regions in the UK, different regimens exist even within regions, owing to lack of consensus in the face of a deficit of evidence from high quality clinical trials.

Suggested formulation based on the NEON trial control group

In the London ODN various options for standardising the formulation were considered. The Core Nutrition Group set up for this purpose concluded that the approach should be evidence-based and any standard formulation adopted should be a regimen tested in the context of an RCT. This process of standardisation is ongoing. A formulation based on the NEON trial has been adopted by the North West London ODN for use in the majority of the preterm population during the transition to establishing enteral feeds (**TABLE 2**).

Rationale for choice of formulation of standard PN

Volumes

These are based on the aqueous volumes used in the NEON trial where intended intake of macronutrients was achieved even after consideration of additional fluids for the delivery of drugs. There is no evidence for the practice of restricting fluid intakes below 90mL/kg/day in the first few postnatal days. Various audits published[10] and unpublished have consistently shown that prescribed nutrient intakes are rarely achieved. The majority of commercially available PN is constituted in large volumes such that it is either not possible to deliver all the nutrition in the early postnatal period or when weaning from PN to enteral feeds.

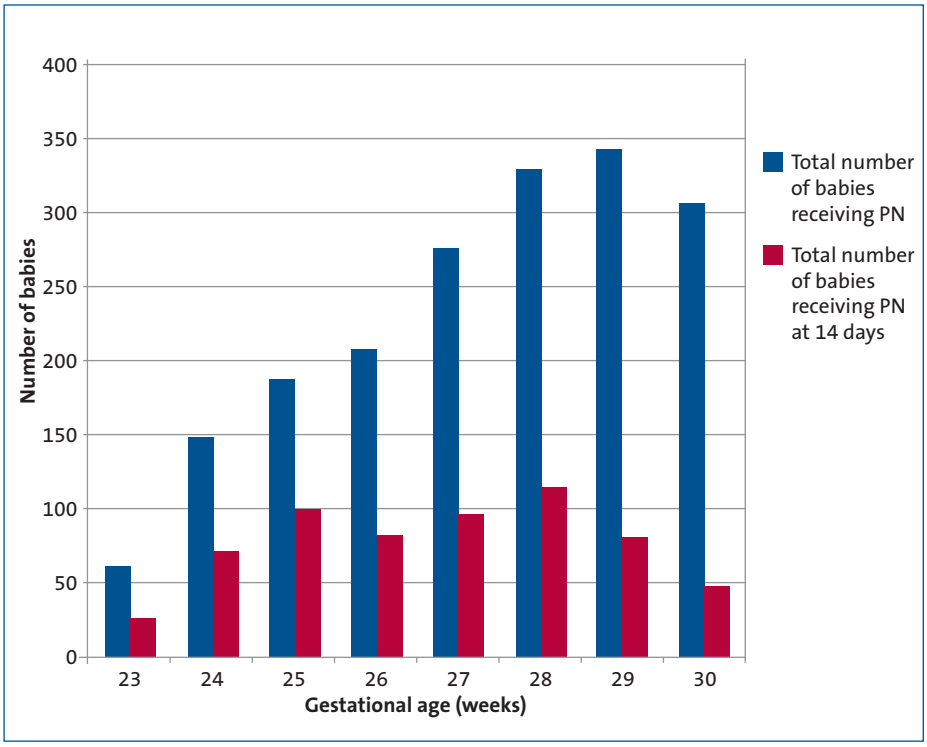

FIGURE 1 The number of infants in the London ODN of <31 weeks' gestation receiving PN, and the number still receiving PN at 14 days by gestational age in 2014 and 2015.

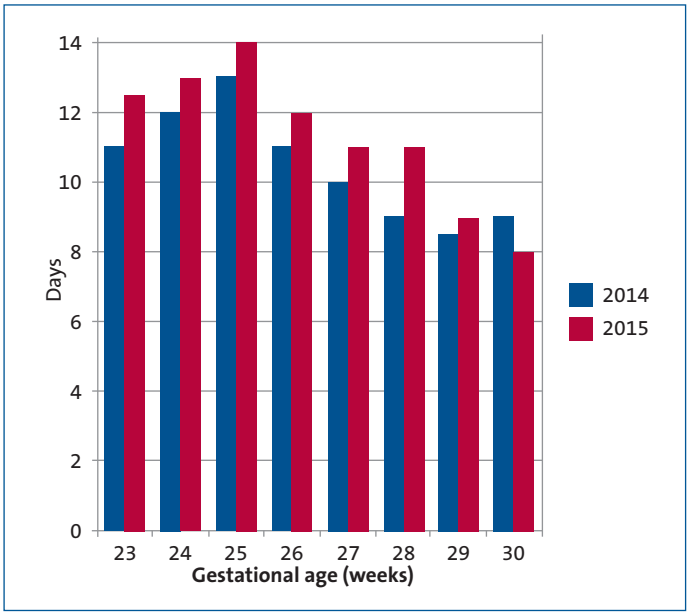

FIGURE 2 The median duration of PN by gestational age in infants <31 weeks' gestation in 2014 and 2015 before establishment of full enteral feeds. Data from NDAU for the London ODN.

The 'start up' aqueous bag is constituted in 90mL/kg/day and may be used on postnatal days 1 and 2. The 'maintenance' aqueous bag is constituted in 120mL/kg/day and may be used from postnatal day two onwards. Lipid volumes are intended to run separate from the aqueous bag. At the maximum intake of 3g/kg/day the lipid rate is 15mL/kg/day without added vitamins and 17mL/kg/day with added vitamins. It is suggested that PN volumes are weaned once an infant is on an enteral intake of 60mL/kg/day.

Carbohydrate

The rationale for an intake of 8.6g/kg/day (6mg/kg/min) is primarily prevention of hyperglycaemia and also to allow for infusion via a peripheral venous cannula. Both of these issues are reasons for infants not receiving intended intakes of macronutrients in the early postnatal period. Hyperglycaemia is associated with increased mortality and morbidity. There is no evidence for a safe and effective method to manage hyperglycaemia,[11,12] ie whether glucose intake should be reduced or treatment with insulin commenced. It would seem sensible to adopt the approach taken in NEON where intake was at the lower end of 'recommended' at 8.6g/kg/day. Trial protocol suggested that if babies became hyperglycaemic with this intake, insulin therapy should be commenced. Despite the lower intake used in NEON, 23% of infants required insulin therapy and overall 17% of infants had levels of blood glucose >15mmol/L. Using continuous glucose monitoring in the first week of life in the NIRTURE (neonatal insulin replacement therapy in Europe) study, 80% of infants had evidence of glucose levels >8mmol/L, and 32% had glucose levels >10mmol/L at more than 10% of the time with a mean dextrose infusion rate of 11.6g/kg/day (8.12 mg/kg/min).[13]

Amino acids

The rationale for using 2.1g/kg/day in the start-up bag and 2.7g/kg/day in the maintenance bag is based on the NEON trial (**FIGURES 3** and **4**).

NEON demonstrated that providing within 24 hours of birth, recommended intake of amino acids of 3.6g/kg/day compared to an incremental regimen of amino acids (1.7g/kg on day 1, 2.1g/kg on day 2 and a maximum of 2.7g/kg/day from day 3) did not benefit lean body mass at term age, measured by whole body magnetic resonance imaging. Of note, in both randomised groups lean body mass and body composition were almost equivalent to that of the healthy term infant.

Unexpectedly, the trial showed significantly smaller head size in the group randomised to receive higher early intake and significantly higher levels of urea. Head circumference at term was smaller in the Imm-RDI group (mean difference: -0.8cm; 95% CI: -1.5,-0.1; p=0.02).

Imm-RDI infants were more likely than Inc-AA infants to have blood urea nitrogen levels greater than 7mmol/L or 10mmol/L, respectively (75% *vs* 49%; p<0.01 and 49% *vs* 18%; p<0.01). In the SCAMP trial very preterm neonates were randomised to receive higher or lower macronutrient (protein, carbohydrate and lipid) intakes, with greater head growth shown in the former group.[7] However, close inspection of SCAMP data reveals that, although the intention was to deliver a parenteral protein intake of 3.8g/kg/day in the intervention arm, this was not intended or achieved until the end of the first week. Actual mean week one total protein and energy intakes in the intervention arm of SCAMP were equivalent to the control (Inc-AA) group in NEON (**TABLE 3**).

Thus it is entirely feasible that protein intakes similar to the incremental group in NEON and the intervention group in SCAMP are more favourable than higher intakes, which may be detrimental. Early parenteral amino acid intakes higher than 3g/kg/day should be used with caution and in the context of RCTs until evidence from long-term neurodevelopmental and functional outcomes is available.

Lipids

The rationale for using 2g/kg/day on postnatal day 1 and 3g/kg/day on postnatal day 2 onwards also comes from the NEON trial. NEON showed that there was no benefit in using SMOF lipid over Intralipid

Reason for temporarily stopping PN infusion	Number of occasions
Hyperglycaemia	4
Hypoglycaemia secondary to extreme fluid restriction	1
Hyponatraemia	1
Hypernatraemia secondary to dehydration	1
Hyperkalaemia	2
Renal failure	1

TABLE 1 The reasons for stopping PN in the NEON trial.

Component	Units	Postnatal day 1 and 2	Postnatal day 2 or 3 onwards
Fluid for aqueous PN	mL/kg/day	90	120
Amino acid	g/kg/day	2.1	2.7
Carbohydrate	g/kg/day	8.6	8.6
	mg/kg/min	6	6
Sodium	mmol/kg/day	2	4
Potassium	mmol/kg/day	1	2
Phosphate	mmol/kg/day	1	2
Calcium	mmol/kg/day	1	1.5
Magnesium	mmol/kg/day	0.2	0.2
Peditrace*			✔
Lipid	g/kg/day	2 (On day 1) 3 (On day 2)	3

TABLE 2 Suggested formulation for postnatal days 1-3 and beyond. *Trace elements.

in intrahepatocellular fat content at term age measured directly using liver magnetic resonance spectroscopy. There was no significant difference in any measured liver function tests between the two groups. The percentage of infants with hypertriglyceridaemia (defined as >2.5mmol/L in the trial) ranged from 25-32% across the groups. This is consistent with recent systematic reviews of intravenous lipid emulsions in the prevention of hepatotoxicity in infants.[14,15] Although the significance of hypertriglyceridaemia is unknown, there was a standard approach to elevated triglycerides within the NEON trial that involved reducing the lipid infusion rate and subsequent infusion rates based on repeat levels of triglycerides.

Electrolytes

It is recognised that some clinicians have concerns about electrolyte intakes in the early postnatal period especially in relation to sodium intake. The addition of sodium in the start-up bag is primarily and crucially to allow the intake of a minimum amount of phosphate. Providing early intake of amino acid without adequate phosphate can trigger severe hypophosphataemia, hypercalcaemia and hypokalaemia and cause release of phosphate from bone by a mechanism akin to the re-feeding syndrome.[16] This same study calculated that to give 1.8-2.3g/kg/day of amino acids, a minimum of 1mmol/kg/day of phosphate is required. Adding 2mmol/kg/day of sodium to PN allows the intake of 1mmol/kg/day via sodium glycerophosphate.

In the NEON trial, PN on postnatal days 1 and 2 provided 2mmol/kg/day of sodium, 1mmol/kg/day of phosphate and 1mmol/kg/day of calcium. From postnatal day 3, intakes were: sodium = 4mmol/kg/day, phosphate = 2mmol/kg/day and calcium = 1.5mmol/kg/day. No adverse impact of giving an additional 2mmol/kg/day of sodium was seen. Despite this early intake of phosphate, the incidence of low phosphate defined as <1.5mmol/L occurred in 37% of infants although there was no significant difference between the two amino acid groups. There were only five cases (3% of all infants) that had calcium levels greater than 3mmol/L.

Suggested weaning of PN

There is wide variability in the weaning of PN while enteral feeds are being established. This has the consequence of variability in nutritional intake as PN cannot be considered in isolation. A suggested approach in the NEON trial was to commence weaning PN only after 60mL/kg/day of enteral feeds was established and to cease PN when 150mL/kg/day of enteral feeds were tolerated for at least 24 hours (**TABLE 4**). **FIGURES 3** and **4** show total macronutrient intakes when following this enteral and parenteral feeding regimen.

Mean week one parenteral and enteral protein and energy intakes

SCAMP intervention arm = 2.8g/kg/day and 74kcal/kg/day

NEON Inc-AA/SO = 2.5g/kg/day and 73kcal/kg/day

Inc-AA/SMOF = 2.7g/kg/day and 81kcal/kg/day

Mean week one intakes in the intervention arm of NEON

Imm-RDI/SO = 3.4g/kg/day and 85kcal/kg/day

Imm-RDI/SMOF = 3.3g/kg/day and 82kcal/kg/day

TABLE 3 Actual mean week one total protein and energy intakes in the SCAMP and NEON trials.

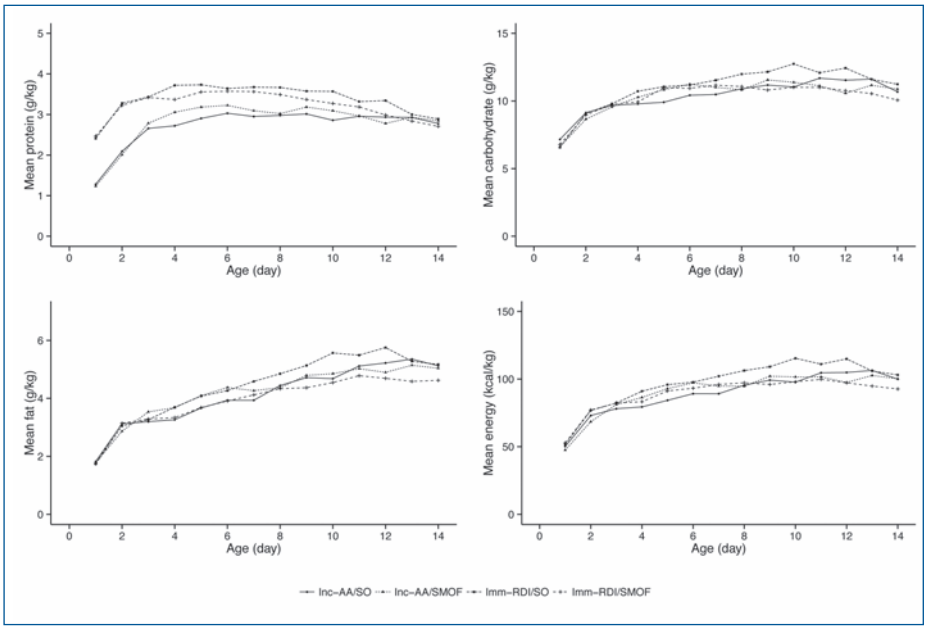

FIGURE 3 Macronutrient intake in the NEON trial over days 1-14.

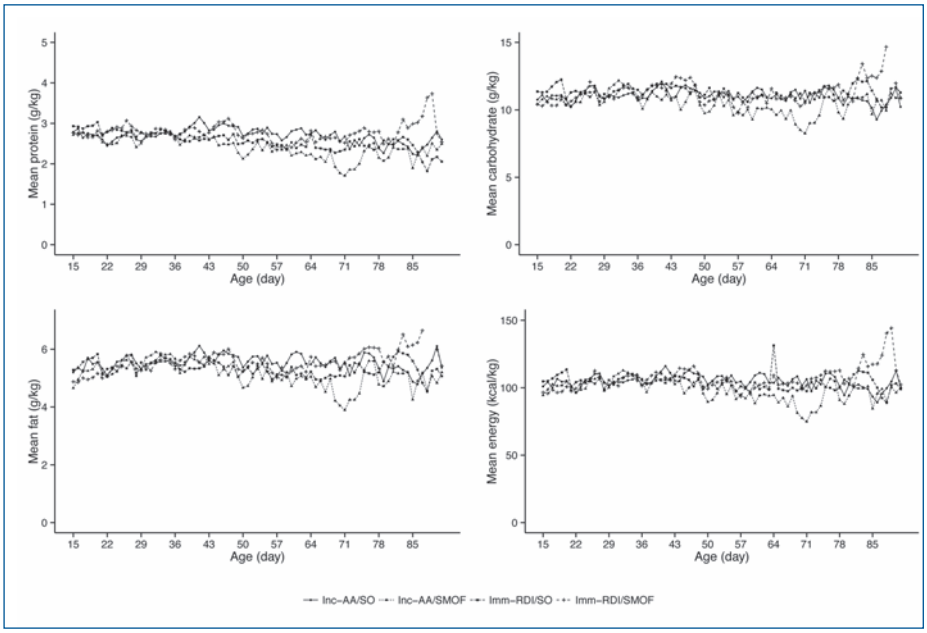

FIGURE 4 Macronutrient intake in the NEON trial day 14 onwards.

Conclusion

Standardised formulations are safe, stable, have a long shelf life and improve the nutritional intake in preterm infants especially in the early postnatal period. In a healthcare system as in the UK they also offer cost-saving opportunities by a process of negotiating a standard price across all neonatal units. Standardisation of formulation should be accompanied by standardisation in the prescription, compounding, dispensing, delivery and documentation of PN. Any change in practice should be accompanied by an audit to establish if intended practice is followed.

Rate of enteral intake (mL/kg /day)	Rate of aqueous infusion, excluding lipid rate (mL/kg/day)	Rate of lipid infusion, with vitamins (mL/kg/day)
60	120	17
65	115	16.5
70	110	16
75	105	15
80	100	14
85	95	13
90	90	12
95	85	11
100	80	10
105	75	9
110	70	8.5
115	65	8
120	60	7.5
125	55	7
130	50	6
135	45	5.5
140	40	5
145	35	4.5
Stop PN when tolerating *at least* 150mL/kg/day of enteral feed for 24 hours	30	4
	25	3.5
	20	3
	15	2
	10	1

TABLE 4 Suggested rates of PN and enteral feeds.

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