Bliss Briefings

The Standardised Concentrated Added Macronutrients Parenteral (SCAMP) nutrition study

[Research findings of a 36 month study into the effects of maximising early nutrition]

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Introduction

It is perhaps not surprising that in the first few days following very preterm birth, both clinicians and parents are preoccupied with the things that immediately relate to survival prospects - usually breathing and circulation. However, it has become much clearer over the last decade that very early nutrition in these babies has much longer lasting consequences than many would have imagined. These consequences are not just for growth but also neurodevelopment and biochemical and metabolic adaptation to life outside the womb. Early nutrition is a challenge because these babies have a bowel that is too immature to digest enough milk for nourishment and therefore rely on intravenous feeding or parenteral nutrition (PN). Technological advances now allow clinicians to administer specially designed neonatal PN through a special drip inserted into the circulation system. This provides the protein and energy (as sugar and fat) needed for growth (the macronutrients) as well as fluid, minerals, vitamins and other 'micronutrients' needed for balanced healthy nutrition. PN buys time to allow the gut to adapt to digesting milk, particularly in the first two weeks of life.

Nutrition, head growth and later neurodevelopment

Despite the routine use of neonatal PN for more than 30 years, it is well recognised that most very premature babies fail to grow properly and this has long-term consequences for growth[1-3]. Of particular importance is head growth, as this is a direct measure of brain growth[4,5]. In a population-based study, babies born less than 29 weeks were shown to have poor head growth for the first four weeks of life, followed by 'catch-up' growth[6]. The presence of catch-up growth suggests early nutritional deficiency. Despite catch-up growth, the expected head growth potential is not achieved[7] and poor early head growth affects later brain growth[8,9] . Following Hack's original work associating head circumference (HC) at eight months with later IQ[10,11], more recent preterm cohorts have reproduced similar findings correlating head growth from birth to discharge with improved neurodevelopmental outcomes at two years[5,12,13] and 4-6 years[13-16]. Studies measuring the early nutrient intake in very preterm babies consistently show nutritional deficiencies when compared to the international recommendations[17-19]. Deficiencies in the protein and energy intake in the first week of life have been associated with poorer neurodevelopmental outcomes[20].

Why do nutritional deficiencies still occur with neonatal PN?

Understandably, in the early days of neonatal PN, clinicians were reluctant to give high quantities of protein, sugar (glucose) and fat (lipid) because of concerns about the effect on the baby's body chemistry and metabolism. Unfortunately, lack of research meant this approach persisted for decades. The survival of more immature babies also increased the complexity of managing body fluids and chemistry and therefore increased the challenge of administering neonatal PN.

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Nutrition was given the lowest priority when there was a need for other intravenous fluids and drugs - as a result, some neonatal PN was not administered to the baby. Lack of adequate research evidence has led to wide variations in clinical practice, prescribing practice and neonatal PN service provision[18-19]. These limitations affected the outcome of a previous PN study evaluating early head growth[21-22] and were highlighted in two recent UK reports[23-24].

Developing the SCAMP nutrition regimen

In 2006 the neonatal and pharmacy teams at the Liverpool Women's Hospital and Royal Liverpool Hospital collaborated on a different approach to neonatal PN formulation, prescribing and administration. The standardised, concentrated, neonatal PN regimen was designed to simplify manufacture, prescription and 'protect' the nutrition from other changes in the fluid and drug management. We showed for the same PN nutrient content, protein intake could be increased by 20 per cent, a remarkable increase in efficiency[25]. We then designed a second formulation to deliver the maximum protein and energy intake recommended for very premature babies. The Standardised, Concentrated Additional Macronutrients Parenteral (SCAMP) nutrition regimen was the result (see Table 1). We designed a study to compare SCAMP and the original regimen (the control)[26].

Table 1: Comparing the nutrient content of SCAMP and control PN (150ml/kg/day)

	SCAMP	Control
Protein (amino acids) g/kg/day	3.8	2.8
Sugar (glucose) g/kg/day	16.2	13.5
Fat (lipid) g/kg/day	3.8	2.8
Energy (kcal/kg/day)	105	85

Primary aim

To compare the difference in head growth (the change in HC, between entering the study and day 28 of life) in babies receiving the SCAMP nutrition regimen and those receiving the control PN.

Secondary aims

To compare SCAMP and control regimens with respect to:

1. Important preterm complications including mortality.
2. Other growth measurements.
3. Infection rates and complication rates of lines in the circulation.
4. Nutrient levels in the blood including blood glucose control.
5. Body chemistry including salt levels (electrolytes) in the blood.
6. Other factors relating to the safe and optimal use of neonatal PN.
7. Neurodevelopmental follow-up at 2-3 years of age.

Methods

All premature babies were started on the control PN as soon after birth as possible - our standard clinical practice at the time of the study. Following parental consent (before day 5), babies born under 29 weeks gestation and weighing less than 1200g were randomly allocated to either stay on the control PN regimen or switch to the SCAMP nutrition regimen. The babies continued to receive their allocated treatment until day 28, when all babies receiving PN would revert back to the control regimen. Neither

clinicians nor parents knew which regimen the babies received (blinding). The babies' HC was carefully measured at study entry and then weekly until 36 weeks corrected gestational age (4 weeks before due date). Other growth measurements including weight were performed at the same time. Detailed information about all sources of fluid, nutrient and drug intake was collected every day for the first 28 days of life. This included nutrient intake from any milk received. Detailed information about laboratory results was also collected every day during this period. Information about all important complications of prematurity up until discharge was also recorded.

Results[27]

The study showed that during the 28 day study period, the SCAMP regimen delivered an average of 8.7g/kg more protein and 188kcal/kg more energy than the control regimen. The actual protein and energy intakes over the first four weeks of life are compared in Figures 1a and 1b.

Fig 1a: Protein intake (g/kg), weeks 1-4

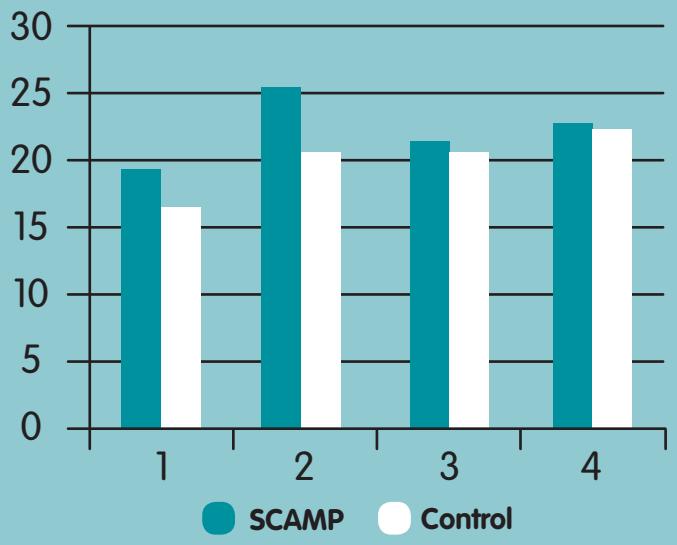
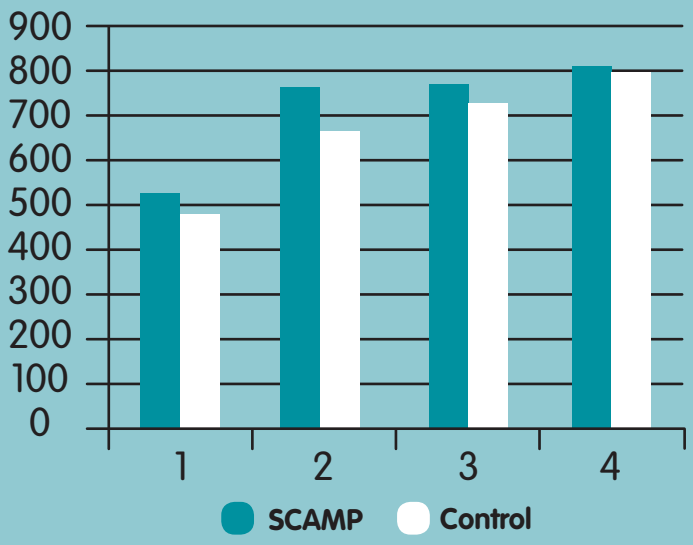
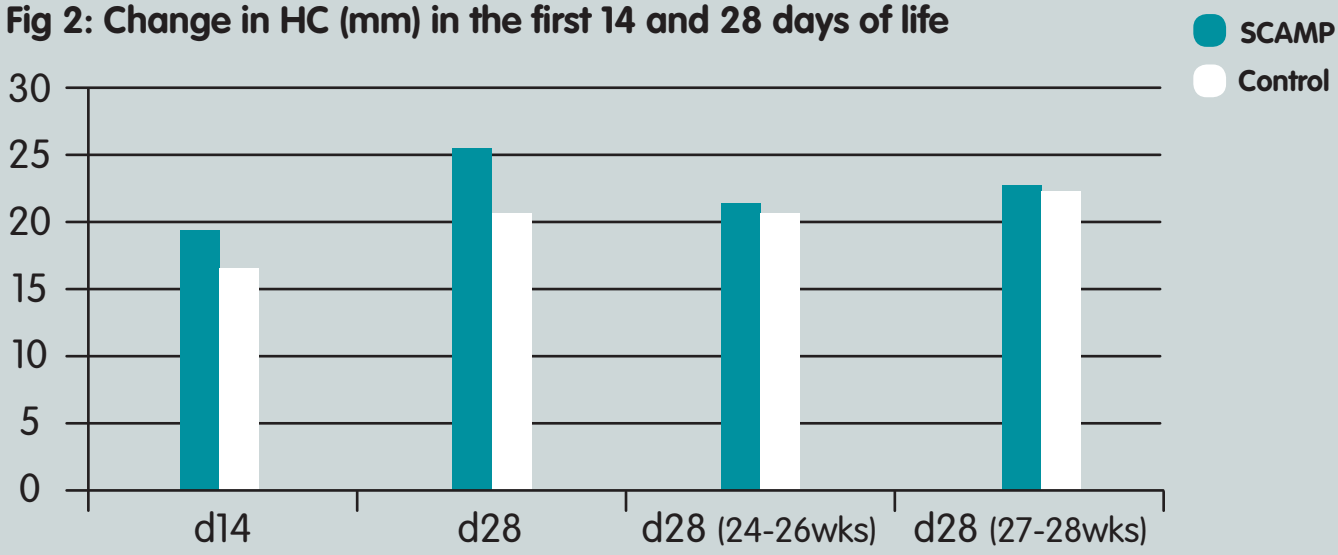


Fig 1b: Calorie intake (kcal/kg), weeks 1-4



The change in HC by day 28 was 5mm greater in the babies receiving the SCAMP regimen than those babies receiving the control regimen (Figure 2). This difference reached a high level of statistical significance ($p<0.01$) meaning that these findings are very unlikely to have arisen by chance. In fact, the difference was already apparent by day 14 of life (see Figure 2). The more premature babies (24-26 weeks gestation) appeared to benefit most.

Fig 2: Change in HC (mm) in the first 14 and 28 days of life



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These findings prove that increasing protein and energy intake using the SCAMP regimen in the first 28 days of life improves head growth. This was the main purpose of the study. Head growth is important because it tells us about brain growth. Using mathematical equations, the 5mm difference in HC achieved with the SCAMP regimen can be translated into an estimated difference of 6 per cent in brain weight.

Head growth was still measured in babies after the study intervention was completed on day 28. After day 28, both SCAMP and control babies received the same nutrition - in fact very little PN is required by this stage, most babies receive all their nutrition from milk. During this period, both SCAMP and control groups demonstrated the catch-up growth described earlier[6]. However, the difference in HC demonstrated between the two groups on day 28 (5mm) persisted, so that at 36 weeks corrected gestational age (CGA) – 4 weeks before due date – there was still a 5mm difference. This indicates that early nutrition interventions improve early head growth and that later catch-up growth does not close the gap.

The SCAMP nutrition study has also provided lots of other very important information:

1. There were benefits for early weight gain in SCAMP babies, although less marked than for head growth[27].
2. There was no difference in mortality or other serious preterm complications when comparing SCAMP and control babies[27].
3. There was no difference in line (drip) infections or other line complications when comparing SCAMP and control babies[28].
4. Despite giving higher amounts of sugar, there were no more problems with blood sugar control in SCAMP versus control babies[29].
5. The improved growth in SCAMP babies was associated with increased requirements for some electrolytes (salts)[30].
6. There is a need to modify the amino acid formulation (building blocks of proteins in PN)[31].

There is still more information to come:

1. More detail about nutrient levels in the blood and body chemistry.
2. Information about the cost-effectiveness of the SCAMP nutrition regimen.
3. Results of the neurodevelopmental follow-up at 2-3 years.

Why are the SCAMP study findings important?

Only by doing randomised controlled trials (studies that allocate babies to one of two treatments by chance) can the benefits of better nutrition be proven. Ultimately, the aim is to prove that optimising PN in very premature babies improves later brain function and neurodevelopment. Very large studies are required to show benefits for later neurodevelopment and intelligence because so many factors can affect this outcome. Such studies take many years and are extremely complex and expensive, particularly in very premature babies. Because of the known relationship between head and brain growth and later neurodevelopment, proving head growth is improved by the SCAMP nutrition regimen is an important first step. It is particularly important to demonstrate that improving early PN has head growth benefits that last long after the premature baby has finished receiving PN. The SCAMP nutrition study provides the evidence required to justify the much larger studies to investigate the effects of PN on

neurodevelopmental outcomes and intelligence in older children who were born very premature. While neurodevelopmental follow-up at 2-3 years is planned in the babies in the SCAMP nutrition study, the study is unlikely to be large enough to show a difference between the SCAMP and control groups.

Will the SCAMP study findings change clinical practice now?

The SCAMP and control PN regimens used in this study both use the same system of PN administration (but with different nutrient contents). The study has shown that the standardised, concentrated neonatal PN concept is an effective way to improve parenteral nutrient intake. The study has provided extensive safety data which has previously been lacking. It is recognised that this approach meets many of the recommendations of the Chief Pharmacists Report on Neonatal PN[24]. The study has also provided reassuring data about the impact of increased nutrition on the body chemistry of very premature babies adapting to life outside the womb. This means that some neonatal services have already implemented similar standardised, concentrated, neonatal PN regimens and others are using the study to develop local versions using the same principles. A group in New Zealand have independently developed a similar neonatal PN strategy[32]. There are regional projects now in place to quantify the cost-effectiveness of this approach. The SCAMP nutrition study has also provided valuable information required to improve neonatal PN formulations (the complex recipe of nutrients and chemicals) in the future.

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