ORIGINAL ARTICLES

Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants

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Abstract

Aims—To improve energy intake in sick very low birthweight (VLBW) infants; to decrease growth problems, lessen pulmonary morbidity, shorten hospital stay, and avoid possible feeding related morbidity. Morbidity in VLBW infants thought to be associated with parenteral and enteral feeding includes bronchopulmonary dysplasia, necrotising enterocolitis, septicaemia, cholestasis and osteopenia of prematurity.

Methods—A prospective randomised controlled trial (RCT) comparing two types of nutritional intervention was performed involving 125 sick VLBW infants in the setting of a regional neonatal intensive care unit. Babies were randomly allocated to either an aggressive nutritional regimen (group A) or a control group (group B). Babies in group B received a conservative nutritional regimen while group A received a package of more aggressive parenteral and enteral nutrition. Statistical analysis was done using Student's *t* test, the Mann-Whitney U test, the χ^2 test and logistic regression.

Results—There was an excess of sicker babies in group A, as measured by initial disease severity (P <0.01), but mean total energy intakes were significantly higher (P <0.001) in group A at days 3 to 42 while receiving total or partial parenteral nutrition. Survival and the incidences of bronchopulmonary dysplasia, septicaemia, cholestasis, osteopenia and necrotising enterocolitis were similar in both groups. Growth in early life and at discharge from hospital was significantly better in babies in group A. There were no decreases in pulmonary morbidity or hospital stay.

Conclusion—Nutritional intake in sick VLBW infants can be improved without increasing the risk of adverse clinical or metabolic sequelae. Improved nutritional intake resulted in better growth, both in the early neonatal period and at hospital discharge, but did not decrease pulmonary morbidity or shorten hospital stay.

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The major cause of mortality in preterm infants is respiratory distress syndrome (RDS), due to deficiency of pulmonary surfactant. However, many survivors develop bronchopulmonary dysplasia (BPD) which can lead to prolonged pulmonary insufficiency, repeated chest infections, and significant risk of death. Exogenous surfactant administration increases the survival of small preterm infants,[1] but improved survival has been associated with an increase in mean duration of stay in neonatal intensive care, and prolonged periods of ventilator dependence.[2] This encouraged us to consider whether nutritional management could influence the outcome of sick very low birthweight (VLBW) (<1500 g) infants.[3]

Initially, a retrospective pilot study was performed to see if undernutrition was a problem in this unit.[4] Mean energy intakes for the first two months of life were significantly lower in 22 infants who developed BPD than for matched ventilated controls; and in both groups these were well below the recommended energy intake of 120 kcal/kg/day.[5] Reasons for this inability to achieve recommended intakes included the need for fluid restriction, intolerance of standard dextrose infusions,[6] and frequent periods of lipid-free alimentation as a result of concerns about respiratory function,[7] hyperbilirubinaemia,[8] and sepsis.[9] The start and attainment of full enteral feeding are often delayed.[4] Technical problems, such as need for non-nutritional fluids, will also decrease nutritional intake. In our experience, it is extremely difficult to achieve the nutritional intake prescribed on a daily basis for sick, as opposed to healthy, VLBW infants.[4]

Poor nutritional intake is compounded by the poor energy reserves of VLBW infants. A baby weighing 1000 g at birth has only 2% of body weight as fat and <0.5% as glycogen compared with 15% and 1.2%, respectively, in

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the term infant.[10] There may also be increased metabolic demands in ventilated VLBW infants, because studies in both ventilator dependent and oxygen dependent babies with BPD have shown that energy expenditure is about 25% higher than in controls.[11] Undernutrition has many effects in the sick VLBW infant. It may cause respiratory muscle fatigue[10] and is implicated in the common problem of growth failure. Lucas *et al*[12] have shown that the early weeks of life are a critical period of neurodevelopment in VLBW infants, during which undernutrition has extremely important adverse effects. Recent work has also shown a link between fetal and infant growth and disease in adult life.[13] Management of the nutritional needs of sick VLBW infants is a controversial area, and there has been a dearth of information derived from randomised controlled trials,[14] particularly in sick infants.

We hypothesised that nutritional intervention could improve outcome in sick VLBW infants and therefore designed a randomised controlled trial comparing aggressive and standard nutritional intervention. The primary objective was to correct energy and nutrient deficiencies. Secondary objectives were to decrease growth failure and pulmonary morbidity, shorten the duration of hospital stay, and to avoid adverse feeding—associated clinical and metabolic conditions. The goal was to provide, but not exceed, the recommended energy intake for growth.[5]

Methods
The study design was a randomised controlled trial. Babies were all those weighing <1200 g at birth, born in or transferred to, a regional neonatal intensive care unit on the first postnatal day, plus those weighing 1200–1499 g requiring mechanical ventilation within 24 hours of birth. Babies were excluded if they had major congenital anomalies. Babies left the study at death or at hospital discharge home. Parental informed consent and approval from the research ethical committee of the Queen's University of Belfast were obtained.

The end points used to calculate sample size were time to regain birthweight, days of oxygen therapy, days of mechanical ventilation and days to discharge from study. We aimed to show a 10% difference in end points. In the absence of any published randomised trials at the time, we used data from the pilot study,[4] a power of 0.8 and a significance level of P <0.05, and a sample size of 100 infants. With an estimated survival rate of 75% for sick VLBW infants, 130 infants were needed. Sample size calculations were performed on the Interstat Package (Department of Medical Statistics, the Queen's University of Belfast).

Babies were assigned to either a group receiving an aggressive enteral/parenteral nutrition regimen (group A) or to a control group (group B). Randomisation was computer generated with stratification to ensure an equal number of extremely low birthweight (<1000 g) and small for gestational age (SGA) (<10th centile weight for gestational age) infants in each group. One hundred and thirty sealed envelopes containing cards indicating group assignation were used for randomisation; there were four separate sets of envelopes to allow for the two by two stratifications. Gestational age was established by menstrual history, early antenatal ultrasound scan, and by Dubowitz assessment.[15] Birthweights were plotted at appropriate gestational ages for each sex on neonatal growth charts (Castlemead Publications, Hertfordshire, England).

NUTRITIONAL REGIMENS
Control group (group B)
These infants were fed parenterally and enterally, in keeping with the then current unit policy[15] which was compatible with the American Academy of Pediatrics recommendations.[5] Fluids were started at 60–80 ml/kg/day and increased to 150–180 ml/kg/d by day 6. Carbohydrate was begun at 4.2–5.5 mg/kg/min on day 1, increasing to a maximum of 10–12 mg/kg/min by day 7. In the event of persistent hyperglycaemia (blood glucose >11 mmol/l with glycosuria ⩾+++ or 55 mmol/l) parenteral glucose was restricted by changing from 10% solution to 5% solution. When hyperglycaemia was corrected (blood glucose 4–8 mmol/l, no glycosuria) parenteral glucose solution was increased from 5% to 7.5% and later to 10% solution.

Amino acid solution (Aminoplasmal Paed, B Braun Medical Ltd) was started at 1 g/kg/day on day 3 and increased by 0.5 g/kg/day to a maximum of 2.5 g/kg/day. Intake was reduced in the event of unexplained metabolic acidosis or blood urea >6 mmol/l. Amino acid solution was stopped when enteral feeds comprised 67% of intake.

Lipid emulsion was introduced as 0.5 g/kg/day of 10% Intralipid (Kabi Vitrum Ltd) on day 5 and increased by 0.5 g/kg/day to a maximum of 2 g/kg/day. Intake was reduced in the event of hypertriglyceridaemia (>1.9 mmol/l) or hypercholesterolaemia (>4.9 mmol/l) and stopped if there were strong suspicions of sepsis, or there was hyperbilirubinaemia (150–250 μmol/l, dependent on weight, age, and clinical status[15]), or when enteral feeds comprised 50% of intake. Lipids were infused for 20 hours a day.

Parenteral minerals were supplied from day 2 of life. Fat soluble vitamins were supplied as an additive to the lipid emulsion (Vitlipid, Kabi Vitrum Ltd). Water soluble vitamins were supplied from day 5 of life (Solvito, Kabi Vitrum Ltd). Trace elements were supplied from day 5 of life (Ped-El, Kabi Vitrum Ltd).

The enteral feed of choice was maternal breast milk. If not available, the mother's choice of preterm formula was used. Enteral feeds were introduced when the infant was clinically stable—that is, respiratory distress was improving and umbilical arterial catheter had been, or was soon to be, removed. Enteral feeds were stopped in the event of respiratory deterioration or abdominal distension. Caloric supplementation of enteral feeds was to a level of 1 kcal/ml using Duocal (Scientific Hospital Supplies, Liverpool), which supplies 40% of energy as fat and 60% as carbohydrate. This

was not controlled in the study. Silicon central venous catheters (Vygon Epicutaneo) were inserted percutaneously where possible if prolonged parenteral nutrition was considered likely. These catheters were removed if bacteraemia occurred and was not responsive to 48 hours of antibiotic treatment.

Intervention group (group A)

These infants received a package of different interventions, which, taken together, constituted a more aggressive parenteral and enteral nutritional regimen. Fluid intakes were similar to the control group. Carbohydrate was also started at 4.2–5.5 mg/kg/min on day 1, but small increments were allowed until parenteral nutrition fluids maximally equivalent to 12.5 % dextrose solution by peripheral catheter or 15% dextrose solution by central catheter were attained. In the event of persistent hyperglycaemia (defined as above), that had not responded to use of 10% glucose solution, continuous insulin infusion (5 U/kg Human Actrapid in 10 ml of 20% albumin and 40 ml of 10% dextrose) was started at 0.05 U/kg/hour (0.5 ml/kg/day) and titrated to achieve normoglycaemia (defined as above). Blood glucose was checked by reagent strips hourly initially and then gradually less frequently, depending on the trend of results. If glucose was <2 mmol/l a plasma glucose sample was checked in the laboratory.

Amino acid solution was started at 0.5 g/kg/day at 12 hours with increments of 0.5 g/kg/day to a maximum of 2.5 g/kg/day (if energy intake <80 kcal/kg/day) or 3.5 g/kg/day (if energy intake is >80 kcal/kg/day). Intake was reduced in the event of metabolic acidosis or blood urea of >6 mmol/l.

Lipid emulsion was introduced at 0.5 g/kg/day on day 2 as 10% Lipofundin MCT/LCT (B Braun Ltd), which is an equal mixture of MCT and LCT, and increased by a maximum of 0.5 g/kg/day to 2 g/kg/day. Strength of emulsion was then changed to 20% Lipofundin MCT/LCT and dose increased by 0.5 g/kg/day to a maximum of 3.5 g/kg/day. Intake was reduced in the event of hypertriglyceridaemia or hypercholesterolaemia. If infection or hyperbilirubinaemia were suspected, lipid intake was reduced to 1 g/kg/day if being infused at a higher level. Parenteral vitamins, trace elements, and minerals were supplied in a similar manner to group B.

Enteral feeds were introduced at 0.5 ml/hour on day 1, regardless of clinical state or presence of an umbilical arterial catheter. They were gradually increased as clinical state improved. In the event of abdominal distension, a quarter glycerine suppository was given. If abdominal distension continued, or there was any suspicion of necrotising enterocolitis, feeds were stopped.

Percutaneously inserted silicone central venous catheters were used if possible, unless parenteral nutrition was considered to be needed only for a few days. Any non-nutritional fluids were given in 5% dextrose if possible and administered at a maximum of 0.5 ml/hour. Parenteral dextrose-amino acid-lipid was supplied in appropriately balanced amounts until full enteral feeding was established.

INVESTIGATIONS

Nutritional intakes were those actually attained, not prescribed, and were recorded at the end of each day. Fluid balance, vital signs, and arterial blood gases were frequently monitored during intensive care. Weight was measured daily; length and head circumference were measured weekly and all were plotted at a corrected age. Blood urea and electrolytes, blood glucose and serum calcium, and full blood count and platelets were measured at least once a day initially, and then gradually reduced in frequency during the period of parenteral nutrition.[15] A parenteral nutrition screen (comprising blood triglycerides, cholesterol, bone profile, renal profile and liver profile) was measured twice weekly during any period of parenteral nutrition. Non-esterified fatty acids and 3-hydroxybutyrate were measured fortnightly in serum (days 1, 14, 28, 42 and 56).

CLINICAL OUTCOMES

It was impossible to blind the group assignation in view of the various interventions possible, so all clinical outcomes were pre-defined, as below. Furthermore, observers of biochemical and radiological end points were unaware of group assignation. Hypoglycaemia was defined as a plasma glucose <2.2 mmol/l. Necrotising enterocolitis was defined as suspicious clinical signs plus gas in the bowel wall on abdominal radiography. Chronic lung disease was defined as the need for supplemental oxygen at 28 days, and BPD as the need for oxygen at 28 days with classic chest radiographic changes. Cholestatic jaundice was defined as a conjugated bilirubin >30 μmol/l for over a week. Osteopenia of prematurity was defined as an alkaline phosphatase value of >1250 U/l with bone demineralisation seen on radiography. Initial disease severity in all babies was retrospectively scored using the CRIB (clinical risk index for babies) score.[16] Transfusions were with 15 ml/kg of packed red blood cells or fresh frozen plasma.[15]

STATISTICS

Normally distributed continuous data were measured using Student's *t* test and other continuous data using the Mann-Whitney U test. Categorical data were analysed using the χ^2 test. These analyses were performed using Statview II software (Abacus Concepts Inc., Berkeley, California). Multivariate analysis was carried out using the statistical package for the Social Services Software Package version 4.0 (SPSS Inc., Chicago, Ill) using logistic regression, forced entry method, with results transformed to odds ratios and 95% confidence intervals of adverse outcomes in each nutritional group.

Results

Enrolment to the study began on 1 April 1990 and continued for 25 months. During this time, 125 babies were enrolled; 64 babies were randomly assigned to the aggressive nutrition

Table 1   Clinical characteristics of 125 babies enrolled

	Group A (n=64)	Group B (n=61)
Mean (SD) gestational age (weeks)	27.0 (2.4)	27.4 (2.3)
Mean (SD) birthweight (g)	925 (221)	933 (242)
No (%) of boys	34 (53)	32 (52)
No (%) being small for gestational age (<10th centile)	19 (30)	19 (31)
No (%) with birthweight <3rd centile	14 (22)	11 (18)
No (%) with maternal steroids	33 (52)	41 (67)
No (%) developing respiratory distress syndrome	39 (61)	34 (56)
No (%) needing surfactant rescue	32 (50)	25 (41)
Median (IQR) initial disease severity measured by CRIB score	6 (3–9)	4 (2–6)*

*P<0.01.
IQR=Interquartile range.

regimen (group A) and 61 to the control regimen (group B). Table 1 shows the clinical characteristics of the 125 babies. There were no significant differences between the groups in terms of mean gestational age, mean birthweight, sex distribution and number who were small for gestational age. There was a tendency for more babies in group A to develop RDS and to require rescue treatment with surfactant. This was also reflected by the significantly higher initial disease severity score (CRIB score) in group A.[16] The CRIB score ranges from a possible score of 0 to 23; a score of 6–10 is associated with a neonatal mortality of about 40%, and a score of 11–15 with a neonatal mortality of 70–75%.[16] In this study the difference in mean CRIB scores between the two groups was due to illness in the first 12 hours of life (maximum negative base excess, minimum and maximum appropriate fraction of inspired oxygen) rather than birthweight (NS) or gestational age (NS). No babies in either group scored due to the presence of con-
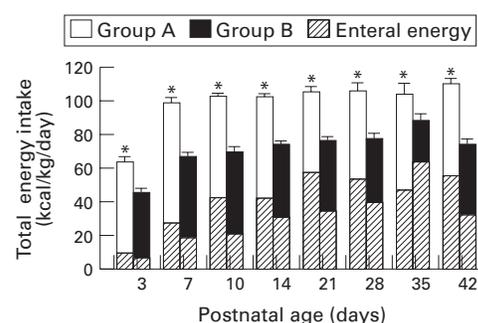

*Figure 1   Mean (SEM) total enteral and parenteral energy intakes (kcal /kg/day) in groups A and B while receiving parenteral nutrition from postnatal ages of 3 to 42 days. * P < 0.001.*

Table 2   Details of carbohydrate, amino acid solution, and central venous catheter use in first week survivors

	Group A (n=51)	Group B (n=54)
Mean (SD) maximum % dextrose solution	13.8 (1.8)	10.4 (1.1)**
No (%) developing hyperglycaemia	18 (35)	24 (44)
No (%) receiving insulin infusion	17 (33)	1 (2)**
Percentage of stay when parenteral nutrition required†	30 (18–40)	31 (21–45)
Mean (SD) % of parenteral nutrition time when amino acids were used	95 (15)	64 (25)**
Mean (SD) maximal amino acid intake (g/kg/d)	3.0 (0.6)	2.0 (0.7)**
No (%) with central venous catheter placed	38 (75)	28 (52)*

*P<0.05.
**P<0.001.
†median (interquartile range).

genital malformations. The CRIB score was calculated for a period before lipid emulsion or amino acid infusion was begun in either group.

FLUID AND ENERGY INTAKES
The mean total energy intakes (enteral plus parenteral) of each group while receiving any parenteral nutrition are shown in fig 1. Babies were excluded from the analysis if they died in the first week of life (n=20) as it was felt that nutritional factors were unimportant in their course; 13 babies died within 48 hours of birth. There were no significant differences in mean fluid intakes between the two groups at any time periods (data not presented). There were significantly higher (P <0.001) mean energy intakes achieved in group A at all time periods while receiving parenteral nutrition (fig 1). Data are available for an extended time period, but after day 42 there were always fewer than 10 babies receiving parenteral nutrition, so results have not been presented.

CARBOHYDRATE AND AMINO ACID RESULTS
Details of carbohydrate and amino acid solution use and central venous catheter use are shown in table 2 for the 105 babies who survived the first week of life. Hyperglycaemia occurred in 42 (40%) of first week survivors and 50 (40%) of all babies. There was no difference in postnatal age or glucose intake at onset of hyperglycaemia in either group. Decisions to violate the protocol with regard to insulin infusion or glucose restriction were clinical, but analysis throughout was on an "intention to treat" basis. There were no episodes of hypoglycaemia during insulin infusion. Parenteral nutrition was used for the minority of the stay (30%) in both groups. Amino acids were infused earlier, in larger amounts and for more of the time of parenteral feeding, in group A than in group B. More babies in group A had percutaneous central venous catheters placed for nutrition (P <0.05) and four babies in each group had these removed for sepsis (NS).

LIPID RESULTS
Babies in group A surviving the first week had significantly higher parenteral lipid intakes (g/kg/day) from day 3 to day 42. For example, the mean lipid intakes in group A and group B were 1.9 and 0.3 g/kg/day, respectively, at day 7; 1.7 and 0.8, respectively, at day 14; 1.8 and 0.6, respectively, at day 28; and 1.7 and 0.4, respectively, at day 35. Table 3 shows that the babies in group A received higher maximal lipid intakes, and for a longer percentage of parenteral nutrition time. Common to many of the results, the control group failed to start lipid as early as planned, and had lower possible lipid intakes, and frequent cessation of lipid emulsion. There were non-significant differences in the mean number of episodes of hypertriglyceridaemia and hypercholesterolaemia per baby between the groups. There were no differences in mean values of 3-hydroxybutyrate or non-esterified fatty acids between the groups at any stage (data not presented).

Table 3   Details of lipid emulsion use in first week survivors

	Group A (n=51)	Group B (n=54)
Duration of lipid (d)†	20 (12–28)	6 (2–15)★
Mean (SD) % of parenteral time when lipid used	89 (10)	29 (22)★
Mean (SD) maximal lipid intake (g/kg/d)	2.4 (0.7)	1.2 (0.7)★
No (%) having lipid stopped	0 (0)	13 (30)★
No (%) with ≥1 episodes of hypertriglyceridaemia	22 (43)	18 (33)
No (%) with ≥1 episodes of hypercholesterolaemia	28 (55)	20 (37)
Mean (SD) maximal bilirubin (umol/l)	174 (41)	177 (38)

†Median (interquartile range).
*P<0.001.

Table 4   Details of enteral feeding in first week survivors

	Group A (n=51)	Group B (n=54)
Time from birth when feed started (d)†	2 (1–2)	5 (3–7)★
Days until full enteral feeding attained†	21 (13–30)	22 (16–30)
No (%) having abdominal distension	28 (55)	31 (57)
No (%) having feeds stopped	14 (27)	33 (63)★
No (%) with umbilical arterial catheter	18 (35)	23 (43)
No (%) fed with umbilical arterial catheter in situ	18 (100)	8 (35)★
No (%) developing necrotising enterocolitis	4 (8)	4 (7)
No (%) using expressed maternal breast milk	15 (30)	23 (44)
No (%) having enteral calorie supplements	18 (35)	13 (25)

†Median (interquartile range).
*P<0.001.

ENTERAL FEEDING

Details of enteral feeding are shown in table 4 and energy intakes from the enteral route in fig 1 for first week survivors. The mean enteral energy intakes were significantly higher in group A at days 3, 7, 10 and 21, reflecting time of starting feeds and incidence of enteral feed cessation. There was no difference in incidence of necrotising enterocolitis between groups and no babies who died in the first week had developed the disease. All umbilical arterial catheters were high (positioned above the diaphragm). The use of enteral calorie supplementation, given to improve poor growth during exclusively enteral feeding, was not controlled in the study.

CLINICAL OUTCOME

The overall survival rate was 76%: 49 babies in group A and 46 in group B. Twenty (67%) of the deaths were in the first week of life and three after 28 days of age. There was no significant difference in median (interquartile range) duration of time in days to death or hospital discharge (61 (24–87) days in group A and 60 (36–86) days in group B). The pre-defined clinical outcomes are shown in table 5. There were no significant differences between groups in numbers of babies developing chronic lung disease, BPD, or needing oxygen at a corrected age of term. Both groups had low incidences of cholestatic jaundice, with one case in group A due to neonatal lupus syndrome, and osteope-

nia of prematurity. There was a trend for lower incidences and mean number of episodes of all documented infections (bacterial and fungal) and coagulase negative staphylococcal infection in group A. Infection was more common in babies who had had central venous catheters placed (P<0.01). These catheters were in place for a median (interquartile range) of 14 (9–19) days.

Post mortem examinations were performed in four cases, three babies being from group A, and there was no evidence of pulmonary arterial lipid deposits. We concluded that in none of the 30 deaths was the nutritional treatment related to the terminal illness of the baby; all deaths were expected, given the clinical situation. Twenty babies died in the first week, all from extreme prematurity or complications of RDS, and had a mean (SD) CRIB score of 12.2 (3.6). The mortality rate for babies with a CRIB > 9 was 78% in this study.

One extremely SGA baby in group A was later diagnosed as having Russell-Silver dwarfism. Details of growth of all babies are given in table 6. Sixteen of the 20 babies (80%) who died in the first week did not regain their birthweight. Change in mean weights in both groups with age are shown in fig 2. Early growth was better in group A with significantly lower mean maximal percentage birthweight loss and median duration of time to regain birthweight. Late growth was relatively better in group A in terms of weight, length, and occipito-frontal circumference.

Adverse outcomes related to growth, respiratory and feeding related morbidities, and mortality are shown in table 7 as odds ratios with 95% confidence intervals. Despite stratified randomisation, group A contained significantly sicker infants at enrolment. Multiple logistic regression analysis was therefore performed to adjust for the effect of the nutritional regimen for the following contributing variables: CRIB score; gestational age (per week); and birthweight (per 100 g). These are expressed as corrected odds ratios with 95% confidence intervals for first week survivors in table 8. The odds of having a growth parameter less than the tenth centile at hospital discharge was more than halved for weight, length, and head circumference (P <0.05). The odds of developing BPD was also halved (NS), and of developing infection was reduced by 70% (P <0.05).
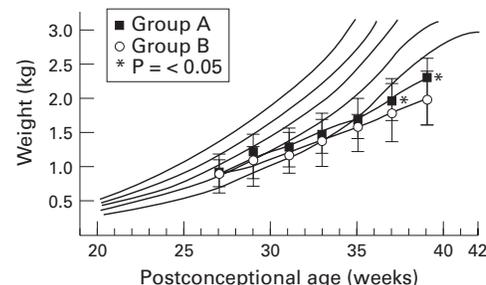

Figure 2   Mean (SD) weight (kg) in groups A and B from birth to postnatal age of 12 weeks, plotted on a Keen and Pearse weight chart for boys.[45]

Table 5   Clinical outcomes of all 125 babies

	Group A (n=64)	Group B (n=61)
No (%) requiring oxygen	59 (92)	52 (85)
Duration of oxygen (d)†	26 (3–48)	19 (3–51)
No (%) requiring mechanical ventilation	54 (84)	47 (77)
Duration of mechanical ventilation (d)†	7 (1–18)	7 (1–18)
No (%) developing chronic lung disease	30 (47)	25 (41)
No (%) developing bronchopulmonary dysplasia	14 (22)	14 (23)
No (%) needing oxygen at term	6 (9)	5 (8)
No (%) developing osteopenia	6 (9)	3 (5)
No (%) developing cholestasis	3 (5)	2 (3)
No (%) developing bacteraemia	32 (50)	40 (66)
Episodes of bacteraemia†	0 (0–1)	1 (0–2)
No (%) developing coagulase-negative staphylococcal bacteraemia	28 (44)	34 (56)
Episodes of coagulase-negative staphylococcal bacteraemia†	0 (0–1)	1 (0–1)
Duration of phototherapy (d)†	4 (2–6)	5 (3–8)*
Transfusions of blood or plasma†	9 (3–15)	10 (5–18)

†Median (interquartile range).
*P<0.05.

Discussion

The aggressive package of parenteral and enteral nutritional interventions resulted in a significantly higher energy intake in sick VLBW infants without an increased incidence of adverse clinical sequelae or metabolic derangement. Although there was a significant improvement in early growth and that at the time of discharge from hospital between the groups, growth remained a problem, overall. It has been reported that most sick VLBW infants have poor weight gain and inadequate catch up growth.[17] A randomised controlled trial of a single nutritional intervention would be easier critically to analyse than this package used in group A, which carries the risk of confounding effects from different interventions within the group.

The mean energy intake while receiving parenteral nutrition was always less than the recommended energy intake for growth of 120 kcal/kg/day,[5] even in group A (fig 1). Nutrient overload, which results in increased fat deposition[18] and pulmonary stress,[19] was unlikely to have occurred. Improved energy intake was never at the expense of increased fluid intakes; high fluid intakes in the first week of life worsen outcome for preterm infants.[20] There was no difference in duration of hospital stay between the groups. At least four factors may have been responsible for this. Despite stratified randomisation, there was an excess of sicker babies in group A, as evidenced by the CRIB scores. This may have been due to lower

Table 6   Early and late growth of all 125 babies‡

	Group A (n=64)	Group B (n=61)
Maximal % weight loss†	5.1 (3.3–8.2)	8.4 (5.5–11.5)*
Time to regain birthweight (d)†	9 (6–11)	12 (9–17)**
Mean (SD) final weight (g)	2111 (904)	2080 (809)
No (%) with weight <10th centile at discharge/death	38 (59)	50 (82)*
No (%) with weight <3rd centile at discharge/death	24 (38)	34 (56)
Mean (SD) final length (cm)	43.0 (6.3)	42.8 (5.9)
No (%) with length <10th centile at discharge/death	36 (56)	45 (74)
No (%) with length <3rd centile at discharge/death	21 (33)	35 (57)*
Mean (SD) final head circumference (cm)	31.4 (5–0)	31.5 (4.5)
No (%) with head circumference <10th centile at discharge/death	9 (14)	18 (30)
No (%) with head circumference <3rd centile at discharge/death	3 (5)	10 (16)

‡Late growth is at discharge or death.
†Median (Interquartile range).
*P<0.05.
**P<0.001.

use of maternal steroid treatment (table 1). The sample size calculation may also have been based on inaccurate estimates because of our use of data from the pilot study.[4] The nutritional management of group B was better than that in either group in the pilot study. This is a form of "Hawthorne effect," where a target of specific attention in a clinical trial is managed better, regardless of the specific nature of any intervention. Enteral nutrition alone was used for a mean of 64% of hospital stay for all 105 first week survivors, and total as opposed to partial parenteral nutrition was used for only a small percentage of hospital stay, so this may have reduced the effect of more energy rich parenteral nutrition in group A.

There has been a good deal of controversy recently about the association between lipid emulsion use and pulmonary morbidity in VLBW infants. A retrospective study showed a seven-fold increase in the incidence of chronic lung disease in babies of 24–30 weeks gestation which was attributed to use of lipid emulsion.[21] A small randomised study concluded that early lipid administration is associated with increased respiratory morbidity in preterm babies.[22] There have been four further published prospective studies[23–26] plus this current study of early parenteral lipid administration to preterm infants. These six randomised studies of 522 sick preterm infants do not show any effect of early lipid administration on the incidence of chronic lung disease. In the current study there was a higher incidence of death in the first week for babies in group A. As stated, all deaths were due to extreme prematurity or pulmonary complications of RDS in extremely sick infants, and 65% of deaths occurred within 48 hours of birth. Sosenko et al[25] had found an increased mortality in a subgroup of infants receiving early parenteral lipid. However, the study has been criticised on methodological grounds, as the subgroup analysis was post-hoc, significantly fewer babies in the early lipid arm of the subgroup had been born after antenatal steroid use, and there was no record of initial illness severity.[26]

Possible mechanisms of lung damage are the production of vasoactive metabolites of lipid emulsion[27] and lipid peroxidation.[28] The fact that mixed MCT/LCT emulsion contains half the amount of linoleic acid is of theoretical benefit. MCT are rapidly and completely oxidised and do not require carnitine for metabolism.[29] Premature infants are deficient in carnitine[30] and this has been suggested as a cause of hyperlipidaemia during parenteral nutrition.

Freeman et al[9] retrospectively investigated possible risk factors for coagulase negative staphylococcal bacteraemia in neonatal intensive care units and concluded that the risk could be attributed primarily to the intravenous administration of lipid emulsions. However, in our prospective study, we have shown that group A, who had significantly greater amounts of lipid, significantly earlier, and for significantly longer percentages of parenteral nutrition, had a trend for lower incidence of coagulase negative

Table 7 Odds ratios (95% confidence intervals) of adverse outcomes in group A (n=64) compared with group B (n=61)

Outcome	Odds ratio (95% CI)
Discharge weight <10th centile	0.3 (0.1–0.7)*
Discharge length <10th centile	0.5 (0.2–1.0)
Discharge head circumference <10th centile	0.4 (0.2–1.0)
BPD	0.9 (0.4–2.1)
Death	0.9 (0.4–2.1)
Death in first week	2.0 (0.7–5.3)
Death or bronchopulmonary displasia	1.0 (0.5–2.0)
Necrotising enterocolitis	0.9 (0.2–4.0)
Bacterial or fungal bacteraemia	0.5 (0.3–1.1)
Coagulase negative staphylococcal bacteraemia	0.6 (0.3–1.3)

*P<0.05.

staphylococcal bacteraemia (44% compared with 56%). Although the incidence of all bacteraemias of 58% seems high, we believe that it is not abnormally high, given that only the smallest, sickest infants were included in this study. By comparison, 80–85% of babies <1000 g had bacteraemia in the study of Sosenko *et al*.[25] Freeman *et al*[9] also implicated the use of central venous catheters as a risk factor for infection. Although infection was more common in babies in this study who had central lines in place, these babies tend to be both the sickest and need parenteral nutrition for the longest durations of time. We have already shown that central venous catheters are not an independent risk factor for bacteraemia in VLBW infants.[31] Notably, significantly more babies in group A had a central venous catheter in place, yet the trend was for a lower incidence of staphylococcal sepsis in this group.

Hyperglycaemia is common in sick VLBW infants[6] and occurred in 40% of babies in this study. It can cause clinically important glycosuria with an osmotic diuresis and thus complicate fluid management. The usual management is to reduce glucose concentration, although this will decrease calorie intake. An alternative is to use insulin, either as a bolus or as a continuous infusion.[32] We have shown that continuous insulin infusion can be a useful treatment option, without causing hypoglycaemia, provided that there is adequate monitoring of blood and urine glucose values to permit accurate titration of insulin dose.

There has also been considerable controversy in neonatology about when to initiate enteral feeding in sick VLBW infants. Due to concerns about exacerbation of pulmonary disease, pulmonary aspiration, and the development of necrotising enterocolitis, it became common practice to feed the sick VLBW infant by total parenteral nutrition only in early life. However, animal studies have shown that enteral intake is needed to maintain small intestinal mass and promote disaccharidase activity.[33] In preterm infants plasma gut hormone surges can be triggered by small amounts of enteral feed, and these are trophic for the gut.[34] In addition to this current study, there have been five reports[35–39] of randomised controlled trials of early enteral feeding, with necrotising enterocolitis as a primary or secondary outcome. These six studies taken together show that early enteral feeding does not increase the risk. Early enteral feeding has also been shown to improve intestinal maturation and feeding tolerance in preterm infants[40] and is not associated with an increased incidence of gastro-oesophageal reflux.[41] Enteral feeds are often withheld when an umbilical arterial catheter is in place, because of concerns about the risk of necrotising enterocolitis. Our study suggests that there is no increased risk when feeds are started with a high umbilical arterial catheter in situ. A small prospective study has shown a similar result for low umbilical arterial catheters.[42]

This study has shown that nutritional intake in the sick VLBW infant can be improved without an increased incidence of adverse clinical or metabolic sequelae. Improved nutritional intake resulted in better growth, both in the early neonatal period and at discharge from hospital, but not reduced pulmonary morbidity or hospital stay. Long term effects on growth and development of these babies are currently being studied. We believe that the improved nutritional intake is clinically relevant, given the prolonged period during which sick preterm infants receive total or partial parenteral nutrition. We also believe that it is imperative to monitor nutritional intake actually achieved, rather than that prescribed, in any nutritional study of VLBW infants. To optimise nutritional intake, the main requirements are increased awareness of potential problems and changes in nutritional protocols. Nutritional management in our regional neonatal intensive care unit has been changed following this study.[43 44]

Table 8 Adjusted odds ratios (95% confidence intervals) of adverse outcomes in first week survivors of group A compared with group B

Outcome	Odds ratio (95% CI)
Discharge weight <10th centile	0.2 (0.1–0.7)*
Discharge length <10th centile	0.4 (0.2–0.9)*
Discharge head circumference <10th centile	0.3 (0.1–0.8)*
Bronchopulmonary dysplasia	0.5 (0.2–1.6)
Death or BPD	0.4 (0.1–1.0)
Necrotising enterocolitis	1.2 (0.2–8.0)
Bacterial or fungal bacteraemia	0.3 (0.1–0.9)*
Coagulase negative staphylococcal bacteraemia	0.5 (0.2–1.1)

*P<0.05.

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