DOI: 10.7860/IJNMR/2013/5234:1988

Original Article

Pathology Section

# The Influence of Parenteral Energy and Protein Intakes in the First Week on the Growth of Very Low Birth Weight Babies

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## ABSTRACT

**Objective:** To compare growth of very low birth weight (VLBW) infants given standard total parenteral nutrition (TPN), providing 25kcal/g amino acids, and high calcium TPN, providing 30kcal/g amino acids. Energy to protein ratio affects protein catabolism. Regimens providing less than 30kcal/g amino acids increase protein catabolism, leaving insufficient for growth.

**Study Design:** All VLBW infants given high calcium TPN during the first 44 months of its use were compared with all those given standard TPN over the previous 24 months. Growth was assessed from mineral retention on TPN and anthropometric measurements until discharge from paediatric follow up. Ignoring stools, mineral retention equaled TPN intake minus urine excretion measured from daily urine samples:

Mineral excretion mmol/kg/day = Urine mineral/ urine creatinine x creatinine production Creatinine production µmol/kg/day = -2.07 + 2.34 x gestational age in weeks.

**Results:** 16 infants fed standard TPN retained less than 1 mmol/kg/day of calcium and phosphate and developed high alkaline phosphatase. TPN increased their protein catabolism. Their neonatal growth in weight and head circumference was retarded affecting their childhood growth.

23 infants fed high calcium TPN retained minerals at optimal rates and maintained normal alkaline phosphatase. TPN did not increase their protein catabolism, unless they received dexamethasone, which improved their breathing, allowing more TPN that prevented nitrogen retention from falling. Their neonatal growth was normal and did not affect their childhood growth. 6 (26%) infants, all below 29 weeks, needed insulin to control hyperglycaemia while on TPN, with normal glucose control in more mature babies.

**Conclusion:** High calcium TPN with 30kcal/g amino acids produces normal growth. Standard TPN with 25kcal/g amino acids increases protein catabolism compromising growth.

**Keywords:** Energy, Protein, Catabolism, Growth, Preterm, Parenteral nutrition

## INTRODUCTION

Nutritional deficiency and early postnatal growth failure are common in very low birth weight (VLBW) infants [1-4]. This has been shown to affect childhood growth and neuro-developmental outcome [5,6] and may increase the risk of adult onset disease [7-9].

These babies are unable to tolerate full milk feeds for days or sometimes weeks after delivery. During this time their growth is sustained by total parenteral nutrition (TPN). Surveys have shown wide variation in parenteral feeding practice with increases in protein intake of 1g/kg/day being associated with increases in growth velocity of 4g/kg/day [10]. Starting TPN in the first few hours of birth has been associated with improved weight gain [11].

The fastest rate of human growth, particularly of the brain, occurs from 24 to 38 weeks gestation. Developmental outcomes at 18 months in extremely low birth weight infants correlate with protein and energy intakes in the first week [12]. At 5 years, cognitive outcomes in VLBW babies were correlated with neonatal weight gain and head circumference growth [13]. Impaired brain growth may also explain why very preterm children, when 6 years old, have increased risk of pervasive emotional problems and inattention/hyperactivity [14] and why the risk of developing attention deficit/hyperactivity disorder (ADHD) progressively increases with the degree of prematurity below 38 weeks gestation [15].

The ratio of energy to protein provided by TPN governs the rate of protein catabolism, which increases when low energy to protein ratios are provided, in order to meet the infant's energy needs. This consumes protein that otherwise could be used for growth and raises

blood amino acids, ammonia and organic acids with potentially deleterious effects [16]. When infants were given an amino acid preparation providing twice as much phenylalanine as they required, at energy protein ratios varying from 17 to 55 kcal/g protein, they only developed plasma phenylalanine above 100 µmol/L when less than 30kcal/g amino acids were given in TPN [17]. This indicates that the lowest energy protein ratio that can be given without increasing protein catabolism is 30kcal/g amino acids. Ratios above this provide insufficient protein for growth.

In 1998 high calcium TPN was introduced into a number of neonatal units in New Zealand. This regimen was designed to provide protein intakes of 3g/kg/day with energy intakes of 30kcal/g of amino acids as well as optimal intakes of all six macro minerals. At the time written invitations to other neonatal units to participate in a multicentre study evaluating this regimen met with no success. As the only alternative, a detailed evaluation was done in the first cohort of infants to receive high calcium TPN in New Plymouth. They were compared with infants receiving the previously used standard TPN providing 25 kcal/g amino acids. This data is now presented in formats that allow comparison with recent multicentre studies [18,19], which have added to the controversy regarding the prevention of postnatal growth failure.

### Design of high calcium TPN

An ideal TPN regimen should provide the right balance of water, glucose, all essential amino acids, lipids, minerals, trace elements and vitamins for the optimal growth of all tissues, without any additives or potential toxins, and without causing fluid, electrolyte or acid base disturbances, infection or other complications.

The ingredients used in high calcium TPN are shown in [Table/Fig-1] and its composition is compared with standard TPN in [Table/Fig-2] and [Table/Fig-3]. This choice of composition was determined as follows.

### Glucose and amino acids

High calcium TPN contained 125g/L of glucose and 24.5g/L of amino acids, which, when given with 17.7% Lipid, produces protein intakes of 3g/kg/day with 30kcal/g of amino acids, the optimal ratio for protein retention (17). Standard TPN contained 100g/L of glucose and 27.17g/L of amino acids, providing only 25kcal/g amino acids when given with 17.7% Lipid.

### Calcium and phosphate

In high calcium TPN, calcium chloride and glucose-1-phosphate, an organic phosphate source, provide sufficient calcium and phosphate to match the intakes VLBW infants would have received in utero during the third trimester of pregnancy [20]. A meta-analysis of mineral balance studies in VLBW infants show that calcium retention (x) is closely related to phosphate retention (y) in mmol/kg/day as follows [21]:

$y = 0.5 + 0.7x$ (n 27, r 0.95)

This is in keeping with phosphate being required both for soft tissue growth as well as bone growth, where calcium and phosphate are deposited in a molar ratio of 10:6. High calcium TPN provided an excess of phosphate to avoid any risks of hypercalcaemia developing in growth retarded babies who have high phosphate requirements [22].

Standard TPN contained only 10mmol/L of calcium and phosphate, the maximum allowed by the solubility of calcium gluconate and potassium phosphate. Two thirds of gluconate in TPN is excreted in urine without being metabolized. Gluconate causes metabolic acidosis by accumulating in plasma as organic acid and by increasing urinary loss of mineral base [16].

### Magnesium

Magnesium is provided by magnesium chloride, rather than magnesium sulphate, because sulphate is not metabolized and, like gluconate, accumulates in plasma as organic acid and depletes mineral base by increasing its urinary loss. The magnesium concentration of 2mmol/L was chosen because concentrations of 2.4mmol/L in standard TPN caused high plasma magnesium, whereas concentrations of 1.4mmol/L resulted in little magnesium retention [22].

### Potassium

Potassium was supplied by potassium acetate, which provided 1mmol for each gram of amino acids, in keeping with the close relation observed between protein and potassium balance in sick preterm babies [22]. In the first 48 hours without TPN 1mmol of potassium was released from cells for each gram of protein broken down to urea, whereas after 48 hours with TPN a similar amount of potassium was retained with each gram of protein. Starting TPN on day 1 produces protein retention and hypokalaemia develops unless potassium is included in TPN. Acetate is fully metabolized and therefore does not contribute to acid base balance.

### Sodium and chloride

Sodium and chloride were provided in equimolar concentrations as imbalances cause acid base disturbance [16]. After 48 hours high calcium TPN provided 5mmol/kg/day of sodium, meeting the requirements of VLBW infants on TPN. Standard TPN regimen contained lower sodium concentrations and all less than 1000g infants given this regimen required additional sodium by day 7 to correct hyponatraemia, whereas no infants given a previous regimen providing 5 mmol/kg/day needed additional sodium.

As shown in [Table/Fig-2], two new TPN solutions were used. The low sodium solution was used in the first 48 hours, when sodium intakes should be minimized, and the high calcium solution was given after 48 hours. The low sodium solution was also used after 48 hours in term babies needing TPN. These two solutions differed only in their macro minerals and not in their glucose, protein, organic acid or trace element composition.

### Administration of TPN

The most important complication of administering TPN to premature babies is infection, which causes both mortality and considerable morbidity, including cholestatic jaundice, venous obstruction and infective endocarditis. Infection reduces protein retention from TPN.

The following TPN policy was used throughout this study to prevent infection. This policy was originally developed at University College, London and had previously been shown to reduce the rate of infection in Brighton, England and later Wellington, New Zealand.

TPN was prepared commercially and, after rigorous stability testing, bags of high calcium TPN were given a shelf life of 3 months. Addition of vitamins to lipid and assembly of fluid administration apparatus was done under strict aseptic conditions in the hospital pharmacy. TPN was administered exclusively through percutaneous central venous catheters (long lines) inserted soon after delivery, prior to skin colonization, and maintained with strict attention to aseptic technique. High calcium TPN should not be given through peripheral IV lines because of the hazards from extravasation of high calcium fluid.

To insert the long line, the baby was nursed under radiant heat on an open area, as breaches in sterile technique are inevitable if this procedure is attempted in a closed incubator. Having measured the distance to insert the catheter from a suitable vein, all attachments and drips were removed from the limb before scrubbing, gowning and gloving up. Aqueous betadine washed off with aqueous chlorhexidine were used to prepare the entire limb, which was then posted through a hole in a sterile drape. Further sterile drapes were applied to a wide area around the baby. Having inserted the long line the desired distance and checked that blood could be freely aspirated, suitable positioning of the tip outside the heart was confirmed radiologically. The line was then carefully secured with adhesive spray and steristrips, to prevent any later movement, before finally covering the whole area with sterile adhesive transparent dressing, which was not taken off until the line was removed.

TPN, including 17.7% Lipid, was initiated as soon as the long line was inserted and no other fluids or drugs were subsequently given through the long line. A 150 cm extension tube was attached to the long line at the time of insertion to allow TPN to be changed every 48 hours at a distance from the baby on a sterile area, again with strict aseptic techniques. No filters were used and TPN did not contain heparin or vancomycin.

TPN was given as maintenance fluid from day 1, with 17.7% Lipid given at one tenth of the rate of the low sodium solution. Total fluids were started at 100mL/kg/day for 24-25 week gestation infants, 80mL/kg/day for 26-27 week gestation infants and 60mL/kg/day for 28 -31 week gestation infants [22]. Infants below 28 weeks were nursed in 80% humidity. The rate of fluid administration over the first 48 hours was altered according to the change in plasma sodium, monitored every 8 to 12 hours, with fluids being increased by 10mL/kg/day for every 1mmol/L rise in plasma sodium above 140mmol/L [22].

## METHODS

High calcium TPN was prospectively evaluated for 44 months following its introduction in 1998 and compared with standard TPN, evaluated over the previous 24 months. During these periods all infants admitted to the neonatal unit at Taranaki Base Hospital, New Zealand, requiring TPN because of respiratory or feeding problems, were studied.

When infants were commenced on high calcium TPN, parents were given written information about the regimen with discussion as necessary and provided a signed copy for documentation in the medical records.

Growth of all infants with birth weights less than 1500g and gestational ages below 32 weeks was measured from mineral balance studies on TPN and weight, head circumference and length/height measurements obtained during the neonatal period and on paediatric follow up for over 10 years. Infants of diabetic mothers and those with major congenital malformations were excluded.

TPN was started on day 1 and records were kept of volumes of TPN, other parenteral fluids and milk given until the infants were fully milk fed. While receiving TPN, urine samples were obtained daily or less frequently and analyzed without delay for Na, K, Ca, Mg, Cl, PO4, urea and creatinine and pH. Arterial or venous blood samples were obtained daily or less frequently for blood gases, lactate, glucose, Na, K. Ca, Mg, Cl, PO4, protein, urea, creatinine and alkaline phosphatase. Any positive blood cultures with clinical and laboratory details and key antenatal, delivery and postnatal events and treatments were documented.

Creatinine production is a relatively constant function of body weight that does not change with postnatal age, but does rise with increasing gestational age, in keeping with the larger muscle mass per kilo of more mature babies [22]. Estimates of creatinine production can therefore be used to measure mineral and urea excretion in mmol/kg/day from spot urine samples as follows:

Mineral excretion= [Mineral] urine/[Creatinine] urine x

Creatinine production

Creatinine production= -2.07 + 2.34 x gestational age (weeks) mmol/kg/day

Mineral retention was measured as intake minus urine output, ignoring stool losses. Mineral intakes from milk were not included in these studies, which were not performed when milk intakes had increased sufficiently to reduce TPN intakes below 100mL/kg/day.

Soft tissue phosphate retention = PO4 retention-0.6 x Ca retention.

Urine urea nitrogen rather than urine total nitrogen was measured, because urea measurements were available clinically. Urea nitrogen balance overestimates total nitrogen balance, because it does not include urine losses of non-urea nitrogen. However urea nitrogen balances may be compared and used as a guide to actual nitrogen balance. Furthermore, under stable conditions, urea excretion equals urea production, which measures the rate of protein catabolism.

Neonatal weight gain was calculated as weight at 28 days minus birth weight divided by birth weight [19].

Growth of VLBW infants given standard and high calcium TPN were compared by expressing each weight, head circumference or height measurement as a percentage of the 50th centile for the postmenstrual age of the child, calculated from the equations in [Table/Fig-4]. These equations were derived from neonatal data (23,24) and childhood growth charts provided by Pfizer Australia Pty Ltd. The fall in growth rate after 38 weeks gestation experienced by infants born at term should not happen in VLBW infants and therefore the equations excluded 39 to 45 weeks measurements and used data up to 38 weeks and 46 weeks onwards. From the growth chart of each child the percentile measurements were determined at 34 weeks, term, 18 months and 4 years old. The small differences between 50th centile for boys and girls did not justify separate gender analysis.

Results were expressed as mean ± sample standard deviation (SD) and analysis performed with standard parametric tests and linear regression analysis.

## RESULTS

Standard TPN was given to 8 girls and 8 boys for a total of 268 days. High calcium TPN was given to 12 girls and 11 boys for a total of 555 days. Three episodes of blood culture positive infection occurred, 2 with Staph epidermidis affecting 1 baby given standard and 1 baby given high calcium TPN. One episode of Staph aureus septicaemia occurred with the same organism isolated from blood and a peripheral IV site showing signs of thrombophlebitis, which was therefore considered the source of this infection. Excluding this episode, the rate of septicaemia complicating TPN was 2.4 per 1000 days.

Six of the 23 (26%) infants given high calcium TPN needed insulin to control hyperglycaemia. Glucose control on high calcium TPN improved with gestational age with lower glucose in more mature infants. Those over 28 weeks had normal glucose control and did not need insulin. Infants on standard TPN also developed hyperglycaemia, which at that time was managed by reducing glucose/TPN intake rather than giving insulin.

Milk, mainly as expressed breast milk, was given as tolerated. From day 0 to day 7, median milk intake was 1.2 mL/kg/day by infants on standard TPN and 2.1 mL/kg/day by those on high calcium TPN. Nutrient intakes from milk were not included in following analysis.

Infants given standard and high calcium TPN had similar mean birth weights and gestational ages, as shown in [Table/Fig-5], where their nutrient intakes from day 0 to 7 and their weight gains at 4 weeks are compared, with data from Beardsall et al., [18] given in addition. Infants on high calcium TPN had significantly higher energy intakes during the first week and achieved significantly greater weight gains at 4 weeks than those on standard TPN.

The nutrient intakes and weight gains of infants less than 30 weeks gestation given standard and high calcium TPN are compared in [Table/Fig-6], with data from Clark et al., [19] given as well. The intake of standard TPN was often limited by rising plasma urea, which was not a problem on high calcium TPN. Both TPN regimens provided about 3 g/kg/day of protein on day 7, but high calcium TPN provided significantly more energy with infants achieving significantly greater weight gains at 4 weeks than those on standard TPN.

[Table/Fig-7] compares the mineral retention rates achieved by infants less than 30 weeks gestation on standard and high calcium TPN. Protein catabolism, measured as urea excretion, increased significantly on standard TPN but did not rise with the intake of high calcium TPN. Urea nitrogen retention was significantly higher on high calcium TPN.

Nitrogen retention on high calcium TPN correlated well with potassium, soft tissue phosphate and magnesium retention, as shown in [Table/Fig-8]. On average 4.48 mmol of potassium, 2.06 mmol of soft tissue phosphate and 0.46 mmol of magnesium were retained with each gram of nitrogen.

Two infants on standard TPN and 7 on high calcium TPN were treated with dexamethasone for chronic lung disease. In infants on high calcium TPN, dexamethasone increased protein catabolism and urine phosphate, but respiratory improvement allowed greater TPN intakes that prevented nitrogen retention from falling, as shown in [Table/Fig-7].

VLBW infants given standard TPN experienced significant postnatal growth retardation evident by 2 weeks old. This failure happened at the time of their most rapid growth and affected their later childhood, as shown in [Table/Fig-9]. Infants given high calcium TPN did not suffer postnatal growth retardation and their prematurity did not affect their childhood growth, as shown in [Table/Fig-10].

Growth parameters expressed as percentages of 50th centile for postmenstrual age of infants given standard and high calcium TPN are compared in [Table/Fig-11]. The percentage weights of infants given standard TPN ranged from 60% to 120%. The range for infants given high calcium TPN was similar, except for one infant with percentage weight below 40%. Data from this child was included in comparisons of changed weight percentages from birth, but was excluded from head circumference and height comparisons.

Weight percentages of infants given standard TPN fell by 15.53% at 4 weeks, recovered a little at 34 weeks, but then fell to 17.73% at term and did not return to normal until after 18 months. Head circumference percentages of infants given standard TPN fell significantly by 4 weeks ($p < 0.01$) and did not recover by term, with normal percentages only being attained by 18 months. Length was not routinely measured until discharge from the neonatal unit, when length percentages were much lower than later height percentages, suggesting that they were underestimated. Height percentages of children given standard TPN were below normal at 18 months and did not recover until 4 years.

Calcium and phosphate retention more than doubled on

high calcium TPN compared to standard TPN, as shown in [Table/Fig-7]. Plasma alkaline phosphatase over the first 14 weeks was significantly higher in infants given standard TPN compared to those given high calcium TPN, who had relatively normal levels, as shown in [Table/Fig-12].

All these children survived and on follow up, 2 that had standard TPN, but none that had high calcium TPN, needed treatment for ADHD.

## DISCUSSION

Protein catabolism increased in VLBW infants fed standard TPN, providing only 25kcal/g amino acids. As a result they retained less nitrogen as well as much less calcium and phosphate than they would have accumulated in utero [20]. They developed postnatal growth retardation affecting their childhood growth and evidence, albeit crude, of bone demineralization with high alkaline phosphatase [25].

High calcium TPN was designed to provide optimal energy, protein and mineral intakes, with 30 kcal/g amino acids. Protein catabolism did not increase on high calcium TPN unless infants were given dexamethasone. This increased protein catabolism, but was offset by improved respiratory status, allowing greater TPN intake that prevented nitrogen retention falling.

VLBW infants fed high calcium TPN did not develop the postnatal growth retardation in weight and head circumference experienced by those on standard TPN. Their childhood growth was unaffected by their very premature birth and none required treatment for ADHD compared with 2 from the standard TPN group [14,15]. They retained nitrogen and calcium at rates comparable to those in utero during the third trimester [20], without developing high alkaline phosphatase. A recent study has confirmed that early high calcium and phosphate intake from TPN prevents bone demineralization [26].

Recent large multicentre randomized controlled trials have failed to establish how best to prevent early postnatal growth failure in very premature babies. A comparison of energy and protein intakes and growth reported from these trials with those on standard and high calcium TPN is revealing.

One American study showed that the low growth rate of below 30 week gestation babies was not improved by increasing their amino acid intake during the first week from 2g/kg/day to 3g/kg/day without providing any additional energy, as shown in [Table/Fig-6] [19]. Insulin use was discouraged and recommended glucose intakes were 8-12mg/kg/min, which should have provided over 50kcal/kg/day. However glucose intakes achieved on day 7 provided only 42kcal/kg/day, in keeping with up to 10% glucose in TPN. Babies given 3g/kg/day of protein received only 25kcal/g amino acids on day 7. They developed higher plasma urea and amino acid concentrations than those on 2g/kg/day of protein, in keeping with the extra protein they received being used for energy production rather than growth. The least mature babies and those treated with dexamethasone had the poorest weight gains. Nutrient intakes and growth on 3 g/kg/day of protein were similar to those on standard TPN, which produced similar elevations in plasma urea. Energy intakes were below those on high calcium TPN.

Another recent American study showed that achieving growth velocity goals and current nutritional practice recommendations for protein but not energy failed to prevent early postnatal growth failure in below 28 weeks gestation infants [27]. TPN was started soon after delivery, achieving intakes on day 7 of 3.5 g/kg/day of protein, 3.1 g/kg/day of fat and 9.3 g/kg/day of glucose, which had produced weight gains above 15 g/kg/day in the first month. However, these intakes provided only 22kcal/g amino acids, which would have caused amino acid catabolism to be increased to meet energy needs, leaving insufficient protein for growth.

Current recommendations are that TPN for very preterm babies should have a high protein content, over 30g/L amino acids, but with only up to 10% glucose [28]. Such high protein content may make up for the energy deficiency as well as provide sufficient for growth. However, a recent report on infants receiving such TPN described increases in blood urea in proportion to the amount of protein given [29]. This means that such regimens increase protein catabolism, thereby increasing blood organic acid [16], amino acid [19] and probably ammonia as well to levels that are potentially harmful particularly during the first few days when there is reduced renal clearance.

The European multicentre study showed that giving under 1500g infants during the first week 0.05units/kg/hour of insulin with 20% glucose to maintain euglycaemia did not improve their 9% mortality rate [18], higher than the 2-3% mortality rate in the first American study [19]. In fact this procedure increased the mortality rate to 14%, increased the risk of hypoglycaemia, particularly in over 1000g infants, and was associated with an increase in the rate of intracranial parenchymal haemorrhages. In both the European and American studies septicaemia affected around 20%, and necrotizing enterocolitis around 10% of infants. No infants studied on standard or high calcium TPN died or had necrotizing enterocolitis, but 8% developed septicaemia.

| Component | Ingredient | Comments |
|---|---|---|
| Amino acids | Vaminolact or Primene | 30Kcal/g amino acids |
| Calcium | CaCl2 | No gluconate |
| Phosphate | Na2glucose-1-PO4 | |
| Magnesium | MgCl2 | No sulphate |
| Potassium | K acetate | 1 mmol/g amino acid |
| Trace elements | Peditrace | Zn,Cu,Se,Mn,I,F |
| Vitamins | Solivito/Vitlipid | |
| Lipids | 20% Intralipid or 20% Clinoleic | |

**[Table/Fig-1]:** Constituents of high calcium TPN

| TPN | | Standard | Low sodium | High Calcium |
|---|---|---|---|---|
| Glucose | g/L | 100 | 125 | 125 |
| Amino acids | g/L | 27.17 | 24.5 | 24.5 |
| Nitrogen | g/L | 3.84 | 3.49 | 3.49 |
| Sodium | mmol/L | 25 | 24 | 39 |
| Chloride | mmol/L | 20.83 | 24 | 39 |
| Potassium | mmol/L | 25 | 25 | 25 |
| Calcium | mmol/L | 10 | 10 | 17.5 |
| Phosphate | mmol/L | 10 | 12 | 19.5 |
| Magnesium | mmol/L | 2.42 | 2 | 2 |

**[Table/Fig-2]:** Composition of TPN regimens

| TPN | | Standard | High calcium |
|---|---|---|---|
| Gluconate | mmol/L | 10 | 0 |
| Sulphate | mmol/L | 1.6 | 0 |
| Acetate | mmol/L | 27.83 | 25 |
| Zinc | µg/L | 324 | 2100 |
| Copper | µg/L | 158 | 168 |
| Selenium | µg/L | 0 | 16.8 |
| Manganese | µg/L | 456 | 8.4 |
| Iodide | µg/L | 42 | 8.4 |
| Flouride | µg/L | 465 | 479 |

**[Table/Fig-3]:** Organic acids and trace elements in TPN regimens

| PMA years | Weight | PMA years | Head circumference | PMA years | Length/height |
|---|---|---|---|---|---|
| 0.3833 - 0.7283 | | 0.3833 – 0.7283 | $47.48x + 0.803$ | 0.3833 – 0.7283 | $74.08x – 2.150$ |
| 0.7283 – 2.2666 | $-3.04x^2 + 14.52x – 5.657$ | 0.7283 – 0.8916 | $-25.21x^2 + 64.11x + 2.077$ | 0.7283 – 0.8916 | $16.46x^2 + 58.69x + 17.78$ |
| 2.2666 – 10.7666 | $0.094x^2 + 1.126x + 8.774$ | 0.8916 – 1.7666 | $-7.948x^2 + 29.12x + 19.64$ | 0.8916 – 2.2666 | $-7.527x^2 + 41.65x + 25.85$ |
| | | 1.7666 – 3.7666 | $0.709x^2 + 5.619x + 38.59$ | 2.2666 – 5.7666 | $-0.633x^2 + 12.79x + 56.32$ |
| | | | | 5.7666 – 10.7666 | $-0.173x^2 + 8.792x + 64.17$ |

**[Table/Fig-4]:** Equations for determining 50th centile for weight, head circumference and height from postmenstrual age in years

| TPN | | Standard | High calcium | | Control | Insulin |
|---|---|---|---|---|---|---|
| VLBW | n | 16 | 23 | | 192 | 194 |
| Gest age | week | 28.1±1.9 | 27.3±1.9 | | 27.8±2.2 | 27.6±2.2 |
| Birthweight | g | 1106±160 | 1026±267 | | 1009±274 | 1007±267 |
| Glucose | Kcal/kg/day | 38.3±4.7 | 49.1±7.4 | <0.001 | 43±10 | 51±13 |
| Lipid | Kcal/kg/day | 10.3±2.4 | 15.9±3.1 | <0.001 | 5.9 (0-13.4) | 5.5 (0-12.3) |
| Protein | g/kg/day | 2.1±0.3 | 2.3±0.4 | | 1.2 (0.2-1.9) | 1.1 (0.2-1.8) |
| Energy | Kcal/kg/day | 56.3±6.1 | 73.5±11.7 | <0.001 | 53.5 | 60.7 |
| | /g protein | 26.9±1.9 | 31.7±1.5 | <0.001 | 43.2 | 54.2 |
| Weight gain | g | 338±110 | 486±117 | <0.001 | 284±138 | 302±146 |

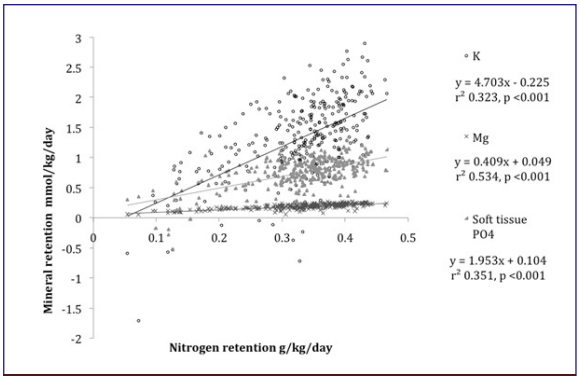
**[Table/Fig-5]:** Comparison of nutrient intake during the first 7 days and 28 day weight gain between standard and high calcium TPN with control and treatment groups reported by Beardsall et al., (65) given comparison

| | | Standard | High calcium | p | 2.5g/kg/day | 3.5g/kg/day |
|---|---|---|---|---|---|---|
| Below 30 wk | n | 11 | 20 | | 58 | 64 |
| Gest age | week | 27.1±1.3 | 26.8±1.6 | | 27 (25-28) | 27 (26-28) |
| Birth weight | g | 1094±175 | 998±273 | | 918 (788-1231) | 961 (780-1187) |
| Glucose | Kcal/kg/day | 48.8±5.8 | 56.5±7.2 | <0.01 | 42 (32-49) | 42.4 (32-51) |
| Lipid | Kcal/kg/day | 17.3±3.3 | 21.1±3.2 | <0.01 | 24 (17-29) | 23 (16-29) |
| Protein | g/kg/day | 3.1±0.5 | 2.9±0.4 | | 2.1 (1.9-2.2) | 3.1 (2.8-3.1) |
| Energy | Kcal/kg/day | 77.6±9.1 | 88.2±11.1 | <0.02 | 73.8 | 76.9 |
| Ratio | /g protein | 24.8±2.1 | 30.5±1.0 | <0.001 | 35.6 | 25 |
| Day 7 urea | mmol/L | 7.2±1.7 | 4.3±1.9 | <0.001 | 7.7 (5-11) | 9.6 (7-13) |
| creatinine | µmol/L | 79±19 | 77±13 | | 88 (65-104) | 80 (62-88) |
| Weight gain | g | 309±83 | 446±105 | <0.001 | 310 (162-448) | 317 (241-443) |
| | g/kg/day | 10.1±2.1 | 17.1±4.9 | <0.001 | 11.4 (7-15) | 12.9 (9-15) |

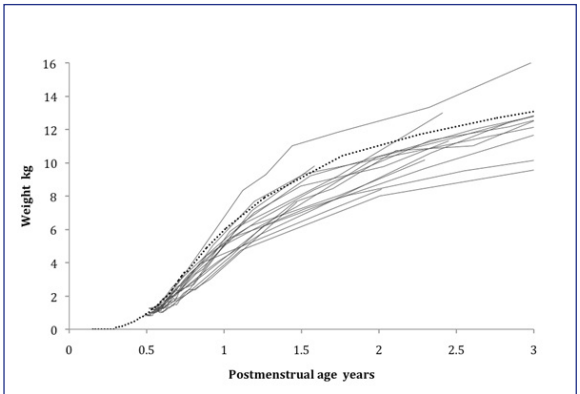
**[Table/Fig-6]:** Comparison of nutrient intake on day 7 and 28 day weight gain between standard TPN and high calcium TPN, with groups receiving 2.5 and 3.5 g/kg/day of protein reported by Clark et al., (63) given for comparison

| TPN | | Standard no steroids | p % | High calcium no steroids | p % | High calcium dexamethasone |
|---|---|---|---|---|---|---|
| Balance studies | n | 37 | | 254 | | 54 |
| TPN intake | mL/kg/day | 99.2 ± 20.1 | <0.001 | 119.2 ± 19.6 | <0.001 | 129.0 ± 11.1 |
| 17.7% Lipid intake | mL/kg/day | 8.3 ± 2.7 | <0.001 | 11.6 ± 2.3 | <0.001 | 13.4 ± 1.3 |
| Nitrogen urine | g/kg/day | 0.125 ± 0.030 | <0.001 | 0.076 ± 0.028 | <0.001 | 0.103 ± 0.042 |
| Nitrogen retention | g/kg/day | 0.253 ± 0.077 | <0.001 | 0.339 ± 0.072 | ns | 0.346 ± 0.055 |
| Potassium urine | mmol/kg/day | 1.403 ± 0.488 | ns | 1.560 ± 0.573 | ns | 1.640 ± 0.576 |
| Potassium retention | mmol/kg/day | 1.077 ± 0.563 | <0.001 | 1.420 ± 0.571 | ns | 1.586 ± 0.641 |
| Phosphate urine | mmol/kg/day | 0.128 ± 0.176 | <0.001 | 0.493 ± 0.220 | <0.001 | 0.738 ± 0.292 |
| Phosphate retention | mmol/kg/day | 0.985 ± 0.343 | <0.001 | 1.999 ± 0.379 | ns | 1.979 ± 0.375 |
| Calcium urine | mmol/kg/day | 0.078 ± 0.063 | <0.02 | 0.059 ± 0.043 | ns | 0.065 ± 0.046 |
| Calcium retention | mmol/kg/day | 0.914 ± 0.167 | <0.001 | 2.024 ± 0.340 | <0.001 | 2.192 ± 0.210 |
| Magnesium urine | mmol/kg/day | 0.079 ± 0.058 | <0.001 | 0.047 ± 0.027 | <0.001 | 0.064 ± 0.036 |
| Magnesium retention | mmol/kg/day | 0.161 ± 0.036 | <0.001 | 0.192 ± 0.040 | ns | 0.194 ± 0.048 |
| Soft tissue PO4 retention | mmol/kg/day | 0.441 ± 0.256 | <0.001 | 0.782 ± 0.227 | <0.01 | 0.687 ± 0.255 |

**[Table/Fig-7]:** Comparison of nitrogen and mineral balances on high calcium TPN with those on standard TPN and with those on high calcium TPN and dexamethasone in infants less than 30 weeks gestation



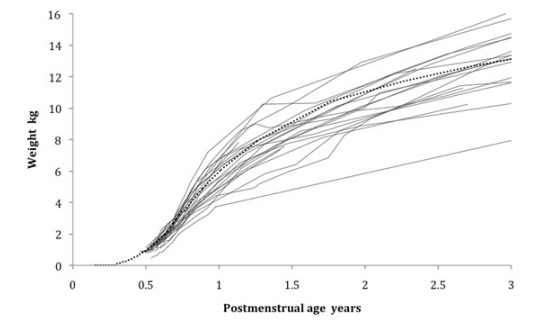

**[Table/Fig-8]:** Retention of potassium, magnesium and soft tissue phosphate correlated with nitrogen retention in 306 balance studies on 20 infants below 30 weeks gestation on high calcium TPN




**[Table/Fig-9]:** Growth in weight of 16 VLBW infants given standard TPN compared to 50th centile for postmenstrual age

As shown in [Table/Fig-5], giving insulin and 20% glucose did increase glucose intakes over the first week, but this did not improve weight gains during the first 28 days (18), which were similar to those in the American study (19). This is not surprising because protein intakes over the first week averaged only 1.1g/kg/day, too low for more energy to be expected to improve growth.

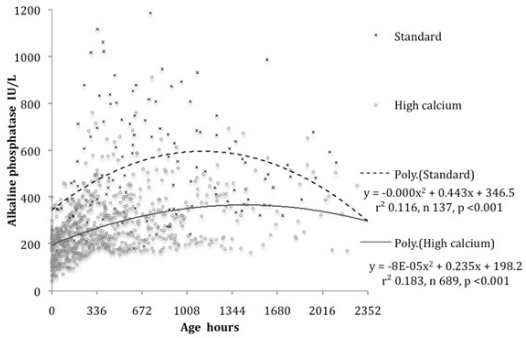
In order to tolerate 12.5% glucose in high calcium TPN, 26% of the VLBW infants needed insulin to control hyperglycaemia. This is not significantly different from 36% of control infants in the European study also needing insulin to control hyperglycaemia, despite being on 10% glucose [18]. Used for this purpose, insulin did not have the risks of causing hypoglycaemia associated with attempts to maintain euglycaemia [18]. Glucose control on high calcium TPN improved with gestational age with normal glucose control in those over 28 weeks. The need for insulin on high calcium TPN appears to reflect relative insulin deficiency in very preterm infants, particularly if growth retarded, rather than an increase from 10% to 12.5% glucose in TPN.




**[Table/Fig-10]:** Growth in weight of 23 VLBW infants given high calcium TPN compared to 50th centile for postmenstrual age

| | TPN | Birth | 4 wks | 34 wks pma | 40 wks pma | 18 months after term | 4 years after term |
|---|---|---|---|---|---|---|---|
| Weight % | Standard | 94.52 ± 17.31 (n 16) | 78.99 ± 12.73 (n 16) | 81.87 ± 13.29 (n 16) | 76.78 ± 11.63 (n 16) | 89.40 ± 11.44 (n 14) | 100.60 ± 23.15 (n 9) |
| change | | | -15.53 ± 8.81 | -12.65 ± 6.78 | -17.73 ± 11.57 | | |
| | High calcium | 96.26 ± 20.53 (n 23) | 89.60 ± 16.11 (n 23) | 93.17 ± 16.00 (n 23) | 91.04 ± 15.80 (n 23) | 96.29 ± 12.13 (n 19) | 106.45 ± 14.43 (n 15) |
| change | | | -6.66 ± 8.72 | -3.08 ± 8.56 | -5.21 ± 13.31 | | |
| | p | ns | < 0.01 | <0.001 | <0.01 | | |
| Head Circ % | Standard | 100.12 ± 5.44 (n13) | 94.96 ± 3.50 (n 16) | 95.85 ± 3.11 (n 16) | 95.91 ± 3.51 (n 16) | 99.55 ± 3.96 (n 14) | |
| | High calcium | 100.34 ± 6.16 (n20) | 97.21 ± 4.51 (n 22) | 97.89 ± 4.84 (n 22) | 98.71 ± 4.06 (n 22) | 100.62 ± 3.47 (n 19) | |
| | p | ns | ns | ns | <0.05 | ns | |
| Height % | Standard | | | | 90.81 ± 4.57 (n 16) | 96.06 ± 3.52 (n 14) | 97.72 ± 8.05 (n 9) |
| | High calcium | | | | 93.21 ± 3.19 (n 22) | 98.21 ± 3.76 (n 19) | 99.69 ± 4.68 (n 15) |
| | p | | | | ns | ns | ns |

**[Table/Fig-11]:** Comparison of growth of VLBW infants given standard and high calcium TPN. Weight, head circumference and height are expressed as percentage of 50th centile for age




**[Table/Fig-12]:** Plasma alkaline phosphatase over the first 14 weeks in VLBW infants given standard TPN averaged 503 ±235 IU/L, significantly higher than 271 ± 123 IU/L in those given high calcium TPN (p <0.001)

## CONCLUSION

TPN providing the optimal energy to protein ratio of 30 kcal/g amino acids, with the optimal amounts of minerals, supports the normal growth of VLBW infants without subjecting them to the risks of increased protein catabolism. A proportion of infants below 30 weeks gestation on such TPN need insulin to control hyperglycaemia, probably because of relative insulin deficiency. TPN providing 25 kcal/g amino acids or less causes protein catabolism to increase to meet energy needs leaving insufficient for growth. TPN with 35 kcal/g amino acids or more does not provide sufficient protein for growth.

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**FINANCIAL OR OTHER COMPETING INTERESTS:**
None.

Date of Publishing: **Oct 31, 2013**