

High versus low amino acid intake at the commencement of parenteral nutrition to improve growth in neonates receiving intensive care (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this review is to determine whether commencement of TPN at higher amounts of amino acid is associated with improved growth and development.

Primary comparison:

1. low vs. high or very high amino acid/protein intake

Secondary comparisons:

1. low vs. high amino acid/protein intake

2. low vs. very high amino acid/protein intake

3. high vs. very high amino acid/protein intake

Sub group analyses (restricted to the primary comparison):

1. Gestational age

a. studies enrolling premature infants (< 37 weeks gestational age)

b. studies enrolling premature infants < 30 weeks gestation

2. Birth weight

a. studies enrolling low birth weight infants (< 2500 grams)

b. studies enrolling very low birth weight infants (< 1500 grams)

3. age at commencement

a. commencement of amino acid/protein containing TPN at < 3 days of age

BACKGROUND

Total parenteral nutrition is widely used to provide nutritional support to sick neonates who are unable to tolerate enteral intake due to prematurity or the nature of their illness. The optimal nutritional goal for neonates should be one that duplicates normal in utero fetal growth rates (AAP 1998). In the first two weeks of life postnatally, the growth rate of extremely low birth weight infants is difficult to measure, as weight changes generally reflect fluid shifts. Glycogen stores are limited and fat mass is insignificant till

the third trimester. Maximal weight specific protein gain occurs before 32 weeks of gestation (Micheli 1993) and the fetus uses amino acids as a major energy source.

Postnatally, nutrition is generally introduced gradually over the first week of life due to concerns of nutrient intolerance by extreme preterms or very ill neonates. Lipid and glucose are used at rates that usually exceed in utero delivery rates, while the amount of amino acid are lower than in utero delivery rates. There are concerns that these neonates are intolerant to protein as evident by

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higher ammonia and blood urea nitrogen levels (Thureen 1999), but higher concentrations of blood urea nitrogen might reflect effective use of amino acids rather than protein intolerance (Thureen 1999). This initial strategy of low amino acids might cause postnatal malnutrition and tends to produce measurable growth failure at hospital discharge (Ziegler 1991; Lucas 1995; Ehrenkranz 1999). Long term developmental outcome may be adversely affected due to low early protein intake (Lucas 1998).

There is evidence that preterm infants have a relatively higher protein turnover rate than term infants (Hay 1996). To obtain optimal protein accretion, a minimum energy intake of 50-60 kcal/kg/day from all energy sources is required. Sufficient energy is required for protein anabolism (Kashyap 1994). When energy availability is limited, nitrogen balance and protein utilization for tissue synthesis is decreased. When protein is used for energy, the amino groups are cleaved and converted primarily to urea which is excreted, while the carbon skeleton enters the citric acid cycle to be used as an energy source. When energy is limited and protein is used as an energy source, maximum protein synthesis cannot occur (Kashyap 1994). Preterm and term infants show an increase of protein synthesis of a similar magnitude with parenteral nutrition and in neither group does increasing the intravenous glucose administration decrease proteolysis despite a threefold increase insulin concentration (Denne 1996). Administering higher rates of amino acid with glucose decreases protein breakdown; 1.5 - 2 g/kg/day of parenteral amino acids is sufficient to avoid a negative protein balance (van Lingen 1992; Rivera 1993; Kashyap 1994a). In the extremely low birth weight infants, achieving intrauterine protein accretion rates may require up to 3.85 g/kg/day of protein (Ziegler 1994).

The benefits of higher protein intake include greater growth of lean tissue, bone and blood constituents, synthesis of hormones and enzymes, and maintenance of oncotic pressure (Fomon 1993). In an animal study, higher protein intake was shown to accelerate maturation of the renal tubules (Jakobsson 1990). Deficiency of protein in infants leads to growth failure, causing oedema and decreased resistance to infection (Nayak 1989).

The risks of higher protein intake include increased concentrations of amino acids (especially tyrosine and phenylalanine), metabolic acidosis, and higher ammonia levels (Senterre 1983; Micheli 1993). This is more pronounced with increasing prematurity. High protein intake could lead to cholestasis and the phosphate content of amino acid solutions may increase the neonates tendency to hypocalcemia (Andronikou 1983). Renal hypertrophy and increased circulating insulin-like growth factor-1 has been reported secondary to high protein intake (Murray 1993). High protein intake in early life may increase the risk of long term obesity and development of diabetes (Rolland 1995; Scaglioni 2000; Raiha 2001). It is, therefore, important to consider the consequences of early nutrition.

OBJECTIVES

The objective of this review is to determine whether commencement of TPN at higher amounts of amino acid is associated with improved growth and development.

Primary comparison:

1. low vs. high or very high amino acid/protein intake

Secondary comparisons:

1. low vs. high amino acid/protein intake
2. low vs. very high amino acid/protein intake
3. high vs. very high amino acid/protein intake

Sub group analyses (restricted to the primary comparison):

1. Gestational age
 - a. studies enrolling premature infants (< 37 weeks gestational age)
 - b. studies enrolling premature infants < 30 weeks gestation
2. Birth weight
 - a. studies enrolling low birth weight infants (< 2500 grams)
 - b. studies enrolling very low birth weight infants (< 1500 grams)
3. age at commencement
 - a. commencement of amino acid/protein containing TPN at < 3 days of age

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised, quasi-randomised trials and randomised cluster trials will be eligible.

Types of participants

All neonates (age < 28 days) admitted to the intensive care unit receiving total parental nutrition (TPN).

Excluded those with metabolic disease affecting protein metabolism.

Types of intervention

Commencement level of amino acid:

- low amino acid/protein intake (< 2 gram/kg/day)
- high amino acid/protein intake (2 - 3 gram/kg/day)
- very high amino acid/protein intake (> 3 gram/kg/day)

Primary comparison:

- low vs. high or very high amino acid/protein intake

Secondary comparison:

- low vs. high amino acid/protein intake
- low vs. very high amino acid/protein intake

- high vs. very high amino acid/ protein intake.

Types of outcome measures

Primary Outcomes: over the first month of life

- Weight gain g/kg/d
- Linear growth cm/week
- Head circumference cm/week

Secondary outcomes:

Biochemical abnormalities: occurring in the first week of life

- Nitrogen balance (Incidence of abnormal serum ammonia and urea levels (mmol/l))
- Incidence of low serum albumin (g/l) < 20 g/l
- Incidence of hypocalcaemia < 2.2 mmol/L and hypophosphataemia < 1.35 mmol/L
- Incidence of metabolic acidosis where the pH < 7.35 and HCO₃ < 12
- During admission to hospital
- Incidence of cholestasis (elevated alkaline phosphatase >450 IU/L, serum level of direct bilirubin > 20% of total serum bilirubin or serum level of direct bilirubin >34 mmol/L)

Other secondary outcomes:

- Incidence of sepsis (positive bacterial culture in CSF, urine or blood)
- Mortality before discharge from hospital
- The total days in oxygen including any oxygen on any part of the day
- Chronic lung disease (oxygen requirement at or beyond 36 weeks corrected age)
- Time to regain birth weight (days)
- Time to full feeds (i.e. when not requiring any IV therapy) in days
- Neurodevelopment at two years (range 18 months to 30 months) defined by standardise neurodevelopmental assessment including incidence of deafness, blindness and cerebral palsy.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Computerized searches will be conducted by two reviewers.. A number of databases will be searched including MEDLINE back to 1966, CINAHL back to 1982, PubMed back to 1966,

EMBASE back to 1988, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library). MeSH headings including infant, newborn, low birth weight, small for gestational age, very low birth weight, premature, amino acids, total parenteral nutrition will be used for the computerized searches. Abstracts, conferences and symposia proceedings from Society of Pediatric Research, and American Academy of Pediatrics will also be identified. Cross references will be reviewed independently for additional relevant titles and abstracts for articles up to 50 years old. Experts will also be contacted to identify other studies relevant to the area.

METHODS OF THE REVIEW

The criteria and standard methods of the Cochrane Collaboration and its Neonatal Review Group will be used. Studies identified in the search will be included if they meet the inclusion criteria .Where there is uncertainty about inclusion of the study, the full text will be retrieved. Data extraction will be performed independently by each reviewer using a structured pro forma; differences will be resolved by discussion. Additional data from unpublished studies in abstract form will be sought from authors of these individual trials if required.

Methodological quality assessment will be based on

- blinding of randomization
- blinding of intervention
- completeness of follow-up
- blinding of outcome measurement.

Statistical analysis will be carried out using the standard method of the Cochrane Neonatal Review Group. Specifically, treatment effect will be expressed as weighted mean difference for continuous variables, and as risk difference (RD) and relative risk (RR) for dichotomous variables. The fixed effect model will be used for meta-analysis with 95% confidence intervals. Meta-analysis will be performed for studies where commencement levels of amino acid is used for similar patients, design and dosage. Tests of between-study heterogeneity (chi-square analysis and I squared) will be used to determine if pooling of data is appropriate; if there is inconsistency in the direction of the effect we will not present the data in the meta-analysis. If I squared suggest heterogeneity, the studies will be consider for sensitivity analysis to identify sources of heterogeneity. Trials will then be excluded one at a time. Funnel plots will be used to identify publication bias. Number needed to treat (NNT) will be determined.

Subgroup analyses (restricted to the primary comparison) will be performed on the following:

1. Gestational age
 - a. studies enrolling premature infants (< 37 weeks gestational age)

- b. studies enrolling premature infants < 30 weeks gestation
- 2. Birth weight
 - a. studies enrolling low birth weight infants (< 2500 grams)
 - b. studies enrolling very low birth weight infants (< 1500 grams)
- 3. Age at commencement
 - a. commencement of amino acid/protein containing TPN at < 3 days of age
- 4. Surgery
 - a. surgery or no surgery performed in the first week of life.

POTENTIAL CONFLICT OF INTEREST

None

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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COVER SHEET

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