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[Intervention Review]

Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease

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ABSTRACT

Background

Preterm infants with bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) have nutritional deficits that may contribute to short and long term morbidity and mortality. Increasing the daily energy intake for these infants may improve their respiratory, growth and neurodevelopmental outcomes.

Objectives

To assess the effect of increased energy intake on mortality and respiratory, growth and neurodevelopmental outcomes for preterm infants with (or developing) CLD/BPD. Secondarily, the review examines any adverse effects associated with increased energy intake.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. This included searches of the Cochrane Central Register of Controlled Trials, MEDLINE (accessed via Ovid), references cited in previous relevant Cochrane reviews and in other relevant studies, review articles, standard textbooks, and manuals of neonatal medicine. Hand search results of the Cochrane Neonatal Review Group were also assessed. Search was updated in December 2010.

Selection criteria

All randomised and quasi-randomised trials comparing the outcomes of preterm infants with (or developing) CLD/BPD who had either increased (> 135 kcal/kg/day) or standard energy intake (98 to 135 kcal/kg/day). Increasing energy intake might be achieved enterally and/or parenterally; enterally by increasing the energy content of the milk, increasing feed volume, or by nutrient supplementation with protein, carbohydrate or fat. The primary outcomes were the development of CLD and neonatal mortality; secondary outcomes included respiratory morbidities, growth, neurodevelopmental status and possible complications with increased energy intake.

Data collection and analysis

We planned to extract data using the standard methods of the Cochrane Neonatal Review Group. Relevant trials would be scrutinized for methodological quality independently by the review authors to determine their eligibility for inclusion. Data of the included trials would be expressed as relative risk, risk difference, NNT and weighted mean difference where appropriate, using a fixed effect model.

Main results

No eligible trials were identified. Fourteen studies that appeared to be relevant were excluded, as no study directly compared increased versus standard energy intakes in infants with CLD/BPD. However, two excluded trials provided some insights into the topic. One study showed that infants with CLD/BPD who were fed formula enriched with protein and minerals had improved growth parameters up until the cessation of the intervention at three months of corrected age. The other study compared different energy density of formula but identical energy intake by setting different feed volumes for both groups. It showed that both groups were unable to achieve the pre-designated feed volumes and that there were no differences in growth, respiratory outcomes, oedema and the diuretic requirements.

Authors' conclusions

To date, no randomised controlled trials are available that examine the effects of increased versus standard energy intake for preterm infants with (or developing) CLD/BPD. Research should be directed at evaluating the effects of various levels of energy intake on this group of infants on clinically important outcomes like mortality, respiratory status, growth and neurodevelopment. The benefits and harms of various ways of increasing energy intake, including higher energy density of milk feed and/or fluid volume (clinically realistic target volume should be set), parenteral nutrition, and the use of various constituents of energy like carbohydrate, protein and fat for this purpose also need to be assessed.

PLAIN LANGUAGE SUMMARY

Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/ chronic lung disease

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is a disease of premature babies who required prolonged support with their breathing and supplemental oxygen. These babies are at high risk of many short and long-term problems with their breathing, growth and development, including death in infancy or childhood. Studies have shown that these babies have higher energy expenditure and lower energy intake compared with babies without CLD/BPD. Increasing energy intake for these babies beyond standard levels may therefore seem beneficial. However, setting high targets for energy intake for these babies may not be achievable. Furthermore, methods of increasing energy intake such as increasing the milk volume or concentration or giving intravenous nutrition may lead to complications of their own. We planned to examine whether increasing energy intake for these babies improves their breathing status, their growth and development, and reduces their risk of death without producing significant complications. Having found no suitable study to date that answers these questions, we are currently unable to provide any evidence on whether increasing the energy intake for babies with (or developing) CLD/BPD is overall beneficial.

BACKGROUND

Description of the condition

Infants with CLD have increased energy expenditure compared to preterm infants without CLD (Denne 2001).This has been attributed to persistent airway inflammation secondary to lung injury from various aetiologies (Pierce 1995) leading to disordered pulmonary mechanics and increased work of breathing (Lui 2000). However, work of breathing cannot completely account for the higher energy expenditure in these infants (Kurzner 1988a). The demonstration of increased pulmonary oxygen consumption has provided new insights into the possible sources of energy expenditure (Schulze 2001). In spite of this increased expenditure in energy, decreased intake is often observed in these infants as a result of poor sucking and iatrogenic fluid restriction (Wilson 1991). Increased energy expenditure and decreased nutrient accretion may account for the perpetuation of their respiratory morbidity, and worsen the growth deficits already experienced by preterm infants after the first few weeks (Embleton 2001). In the long-term, CLD is a risk factor for growth failure (Kurzner 1988b), respiratory morbidities (Northway 1990), and neurodevelopmental disabilities (Singer 1997). These morbidities are compounded by the use of corticosteroids, which have been shown to have at least a temporary growth retarding effect during the course of treatment (Leitch 1999) and a possible association with increased rates of abnormal neurological examination and cerebral palsy (Halliday 2004a).

Despite advances in perinatal and neonatal care over the past decades, chronic lung disease (CLD) has remained a significant complication in preterm and extremely small infants (Parker 1992; Horbar 2002). The current choices of treatment for CLD are either not consistently effective, or are possibly associated with concerning adverse effects (Ng 2004; Suresh 2004; Darlow 2004; Halliday 2004a; Halliday 2004b).

Description of the intervention

Along with other treatments, the addition of certain nutrients or an increase in the overall energy intake for infants with CLD may be beneficial in decreasing these adverse effects and improving outcomes. There are now many studies assessing the role of specific nutrients like vitamin A and antioxidants in CLD (Darlow 2004; Suresh 2004). Less clear is the role of an increase in overall energy intake; there has not been any evidence-based recommendation on the optimal energy intake for infants with CLD (Atkinson 2001).

How the intervention might work

To increase energy intake enterally, one can increase the energy content and/or the volume of feed. In infants with CLD, increasing fluid volume is an issue of concern as there is evidence that restricted fluid intake early in life in very low birth weight infants possibly reduces the risk of developing CLD compared with liberal fluid intake (Bell 2004). Parenteral nutrition alone does not provide adequate energy to meet the needs of preterm infants, and there have been reports associating the use of parenteral nutrition with the development and worsening of CLD (Hammerman 1988; Cooke RW 1991). Compared with fat-based supplements, feeding infants at increased energy level with carbohydrate as the main non-protein fuel confers benefits in better weight gain and net protein accretion, but also produces some less desirable metabolic consequences including higher energy expenditure and O_2 consumption, higher CO_2 production and increased cardiorespiratory work (Kashyap 2001). Other reported complications with various strategies to provide increased energy feeding were feed intolerance, necrotising enterocolitis, symptomatic PDA and sepsis (Sutphen 1988; Schiff 1993; Lucas 1996; Donnell 2002; Hallstrom 2003).

Although the definition of optimal growth for preterm infants is still subject to debate (Cooke RJ 2003), recommendations have been made on their energy intake. Currently, the standard energy intake for a newborn is commonly accepted as 120 kcal/kg/day and recommendations for preterm infants from different authorities range from 98 kcal/kg/day to 135 kcal/kg/day (Klein 2002). This range of energy values was found by different studies to be required to cover for variations in the energy expenditure of preterm infants while providing sufficient energy to approximate intrauterine growth rates (Klein 2002) and could hence be regarded as standard range of energy intakes. Energy levels beyond this range were used to achieve greater growth than intrauterine rates or to compensate for deficits, and could be considered as increased intakes. Currently, the maximum achievable energy intake for preterm infants with positive benefit-risk balance is not known (Klein 2002). The definition of "standard" and "increased" intakes will probably change with changes in the definition of standard growth for preterm infants. A fluid limit of 150 ml/kg/day is assumed when making nutritional recommendations, although some in practice raise the limits up to 180 to 200 ml/kg/day (Klein 2002). The differences in the energy contents of feed and in fluid regimes lead to variations in the working definitions of standard and increased energy intakes. These intakes may not be consistently achieved in practice (Carlson 1998).

Why it is important to do this review

This review aims to examine the effect of increased energy intake on mortality, respiratory, growth and neurodevelopmental outcomes for preterm infants with (or developing) CLD. We also assess whether increased energy intake in these infants is associated with significant complications.

OBJECTIVES

To evaluate the effect of increased energy intake compared to standard energy intake on mortality, respiratory parameters, growth, and neurodevelopmental outcome in preterm infants with (or developing) chronic lung disease/bronchopulmonary dysplasia.

In these infants, is increased energy intake associated with any significant complication compared to standard energy intake?

Subgroup analysis will be performed if available for the following:

1. trials using enteral and/or parenteral methods of delivering increased energy intake;
2. trials using standard fluid volumes and increased fluid volumes to achieve increased energy intake;
3. trials providing additional energy using predominantly protein, carbohydrate or fat, or mixtures of equal proportions (in terms of caloric values);
4. infants with established CLD/BPD and those considered as developing CLD/BPD (as detailed in Types of Participants).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi randomised controlled trials.

Types of participants

Preterm infants (< 37 completed weeks of gestation) with or who are developing BPD/CLD.

Infants considered as having BPD/CLD should fulfil the following criteria:

Oxygen dependence at 28 days after birth or at 36 weeks postmenstrual age and/or typical chest x-ray changes.

Infants considered as developing BPD/CLD should fulfil the following criteria:

1. less than 14 days of life at recruitment;
2. oxygen dependent including those who are ventilated.

These criteria are set so there will be sufficient periods of intervention for the assessment of clinically important outcomes, such as days on oxygen and CLD at day 28 or at 36 weeks postmenstrual age.

Types of interventions

Feeding practice aiming to deliver increased energy intake compared with standard feeding practice.

Increased energy feedings may include any of the following approaches:

1. enteral feeding using energy-enriched formula or fortified breast milk with the same feed volume as the control group. Energy-enriched formula or fortified breast milk should contain energy value higher than that of the standard preterm formula (80 kcal/100 ml);
2. enteral feeding using higher feed volume than the control group, with either energy-enriched formula, standard preterm formula, fortified or unfortified breast milk or standard term formula, alone or in any combination. The targeted feed volume in the experimental group should exceed 150 ml/kg/day;
3. enteral feeding using nutrient supplements to boost energy intake in addition to the standard feeding regime. Nutrient supplement can be given in the forms of protein, carbohydrate, fat or a mixture;
4. parenteral feeding alone;
5. enteral and parenteral feeding combined, in any proportion.

The targeted level of increased energy intake will be accepted as variously defined by the authors of the included trials but must be greater than 135 kcal/kg/day.

Standard energy feeding:

The targeted level of standard energy intake will be accepted as variously defined by the authors of the included trials. However a range between 98 to 135 kcal/kg/day will be set to avoid the inclusion of studies with unusual practices.

The intervention may commence as soon as the infant is considered to be developing BPD/CLD, as detailed in "Types of participants". For trials assessing long term outcomes like growth and neurodevelopment, the intervention may commence before or after discharge. The intervention should be given for at least one month.

Types of outcome measures

Primary outcomes

1. Number of infants with CLD at 28 days after birth or at 36 weeks postmenstrual age.
2. Neonatal mortality (mortality within 28 days of life).
3. Number of infants with CLD or neonatal mortality.

Secondary outcomes

Secondary outcome measures

4. Other short term respiratory outcomes including:

i) days on oxygen;
ii) days of assisted ventilation;
iii) number of extubation failures (re-intubation within 24 hours of prior extubation);
iv) number of infants with pneumothorax;
v) number of infants needing additional treatment for BPD/CLD (steroid, bronchodilators);
vi) number of infants needing home oxygen.

5. Combination of relevant outcomes including:

i) days on oxygen in survivors beyond 28 days of life;
ii) days of assisted ventilation in survivors beyond 28 days of life;
iii) number of infants with pneumothorax and/or neonatal mortality;
iv) number of infants needing additional treatment for BPD/CLD (steroid, bronchodilators) or neonatal mortality;
v) number of infants needing home oxygen or neonatal mortality.

6. Long term respiratory outcomes, including the likelihood of wheeze or asthma (assessed during the follow-up periods of the included studies).

7. Growth: weight, length and head circumference at term and at discharge, and longer term growth including weight, height and head circumference assessed at 6 to12 months of corrected age, or at 12 to 18 month of corrected age and beyond.

8. All cause mortality (during the follow up periods of the included studies).

9. Neurodevelopmental disabilities at or after 12 months of corrected age, assessed using validated tools like Bayley Scales of Infant Development, including diagnosed cerebral palsy, blindness or deafness.

10. Mortality or neurodevelopmental disabilities.

11. Cognitive and educational outcomes at school age (more than five years old), assessed using intelligence quotient and/or indices of educational achievement measured using validated assessment tools, including school examination results.

Possible complications associated with increased energy intake, as follows:

12. Feed intolerance, including gastroesophageal reflux (diagnosed clinically, or via upper GI contrast studies or pH probe studies).

13. Necrotising enterocolitis - any stage, as defined by Bell criteria (Bell 1978).

14. Sepsis (bacterial and fungal - proven by blood culture).

15. Patent ductus arteriosus (echocardiographically proven or clinically diagnosed and treated).

16. All other parenteral nutrition and central line associated complications, including thromboembolism, pericardial tamponade (diagnosed with doppler ultrasound and echocardiography respectively), TPN extravasation and thrombophlebitis (diagnosed clinically).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group, including electronic searches of PubMed (National Library of Medicine) and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 1, 2009). Searches updated February 5, 2009 and again in December 2010.

Our search strategies via PubMed (National Library of Medicine) and CENTRAL are included in Appendix 1 and Appendix 2 respectively.

The studies were accepted whether published or unpublished, in full article or abstract form, as long as assessment of study quality was possible and where the other inclusion criteria were fulfilled. If studies were published as abstracts, the authors would be contacted for further information.

Authors of all studies identified to be relevant would be contacted where possible to clarify details of reported follow up studies where necessary, or to obtain any information about long term follow up where none had been reported and to enquire about additional studies potentially suitable for inclusion.

We examined references cited in previous relevant Cochrane reviews, in other relevant studies, review articles, standard textbooks and manuals of neonatal medicine. Hand search results from the Cochrane Neonatal Review Group were also assessed. Relevant information from expert informants on additional published and unpublished studies was also sought.

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp).

Data collection and analysis

We used the standard methods of the Cochrane Collaboration and its Neonatal Review Group.

Selection of studies

LNM screened the search output , and KTAN obtained full articles for all potentially relevant trials. All three review authors independently assessed these full articles and determine their eligibility using a form with predefined inclusion criteria. Studies that did not fit the criteria were excluded. Any disagreement was resolved by discussion leading to a consensus.

Data extraction and management

Both review authors (LNM and KTAN) would independently enter individual data from each included trial using a standardised data collection form. The data entered would be compared, and differences resolved by consensus. The authors of the relevant trials would be contacted if additional data was required.

Assessment of risk of bias in included studies

If eligible studies were identified, two review authors (LNM and KTAN) planned to independently assess the methodological quality of the included trials using the standard methods of the Cochrane Neonatal Review Group. Specifically, the trials would be assessed on the following: allocation concealment, blinding of intervention, completeness of follow up, intention to treat analysis, blinding of outcome measurement and other information like being single or multicentred. This information would be recorded in the table 'Characteristics of Included Studies' and the 'Risk of Bias' table. The authors of the relevant trials would be contacted if additional information was needed to assess the methodological quality.

Measures of treatment effect

Statistical analysis would follow the procedures of the Cochrane Neonatal Review Group. For categorical data, relative risk, risk difference and NNT would be used with their respective 95% confidence intervals. For continuous data, mean difference would be used with 95% confidence interval. If appropriate, meta-analysis of the included trials would be performed with RevMan 5, using a fixed effects model.

Assessment of heterogeneity

The treatment effects of individual trials and the heterogeneity between trial results would be assessed by inspecting the forest plots. I^2 test would be used to measure inconsistency in the studies' results. If significant heterogeneity was detected, the causes would be explored (for example, difference in study quality, participants, intervention or outcome assessment) via post hoc subgroup analyses.

Data synthesis

If appropriate, we planned to perform meta-analysis using Review Manager software (RevMan 5) supplied by the Cochrane Collaboration. For estimates of typical relative risk and risk difference, we planned to use the Mantel-Haenszel method. For measured quantities, we planned to use the inverse variance method. If appropriate, meta-analysis of the included trials would be performed using a fixed effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed if available for the following:

1. trials using enteral and/or parenteral methods of delivering increased energy intake;
2. trials using standard fluid volumes and increased fluid volumes to achieve increased energy intake;
3. trials providing additional energy using predominantly protein, carbohydrate or fat, or mixtures of equal proportions (in terms of caloric values);

4. infants with established CLD/BPD and those considered as developing CLD/BPD (as detailed in Types of Participants).

RESULTS

Description of studies

Twelve studies were first identified that appeared to be relevant. In an updated search performed in December 2010, two additional relevant studies were identified. Searches performed in the major clinical trial registries (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp) revealed no additional relevant completed or on-going studies. Among the fourteen short listed studies, twelve were published in full text and two as abstracts (Brunton 1998b; Atkinson 1999). Two reports were found to emanate from the same study (Brunton 1998a; Brunton 1998b), hence they are discussed together. After scrutinising all fourteen studies, no studies were found to be eligible for inclusion. These studies are tabulated in the table 'Characteristics of excluded studies'. Six out of the fourteen studies assessed energy intakes in preterm or VLBW infants or infants with (or developing) CLD/BPD, and hence were found to be more relevant than the rest. They are described in more detail as follows:

Atkinson 1999 randomised 70 premature infants with birth weight < 1800 g to either a nutrient-enriched formula or standard formula just prior to discharge with follow up to 12 months of corrected age. Although not explicitly stated, infants with CLD/BPD were excluded as inferred by the exclusion criteria of "severe lung disease".

Brunton 1998a randomised 60 preterm infants with bronchopulmonary dysplasia to either nutrient enriched formula (90 kcal/100 ml, high-protein, high mineral) or standard formula with the same energy density with outcome assessment performed at three months corrected age. The study took place between January 1991 and November 1994. Brunton 1998b, although published one year earlier (1997) in abstract form, was a follow up study to Brunton 1998a. In this study, the same group of infants were followed up until 12 months of corrected age after their nutritional intervention ceased at three months corrected age. The two groups of infants were not allocated to receive different feed volumes, hence their overall energy intakes were not designed to be different. During the follow up-period after three months of corrected age, the overall energy intakes for the participants were also not controlled or compared.

Fewtrell 1997 randomised 60 preterm infants who were still in oxygen at 28 days of age to either high-density formula (100 kcal/100 ml) at 145 ml/kg/day or standard preterm formula (80 kcal/100 ml) at 180 ml/kg/day. Although the results showed a difference in the mean total energy intakes between the high energy group and the standard-energy group (143.3 kcal/kg/day versus 130.5 kcal/kg/day), the intended energy intake for both groups was 145 kcal/kg/day.

Sosenko 1993 randomly assigned 133 ventilator-dependent premature infants to either early intralipid (< 12 hours of life) or to control group (intralipid after day seven). The study was not designed to compare different levels of energy intake.

Wilson 1997 randomised 125 sick VLBW babies to either a standard nutritional regimen or a more aggressive intervention: either earlier and/or more rapid increment of parenteral carbohydrate, amino acids, lipid and enteral feeds. The study was not designed to compare different levels of energy intake. Although the results showed a difference between two groups in their mean energy intakes, the intakes for all babies were consistently lower than 120 kcal/kg/day.

The other studies identified during our search include Brownlee 1993; Pereira 1994; Alwaidh 1996; Carlson 1996; Guzman 2001 and O'Connor 2003. They are listed with the reasons for their exclusion in the table 'Characteristics of excluded studies'.

Risk of bias in included studies

Not applicable.

Effects of interventions

No eligible trials were identified.

DISCUSSION

No randomised controlled trial to date has evaluated the outcomes of preterm infants with (or developing) CLD/BPD who are given increased energy intake versus those with standard energy intake. However, insights were provided by some of the studies that could not be included.

In Brunton 1998a, VLBW infants with CLD/BPD who reached 37 weeks postmenstrual age were randomised to receive one of two formulas, both with identical high energy content at 90 kcal/100 ml, but one enriched with protein and minerals. The enrolled infants were fed the assigned formulas according to the nursery protocol while still in hospital and were fed *ad libitum* after discharge home until three months of corrected age. Outcome assessments were performed at one and three months of corrected age. It was found that the experimental group with enriched protein and minerals in their feed had significantly higher daily intakes of protein, calcium, phosphorus and zinc at one and three months. They also had greater length, lean body mass and bone mineral content, with greater nitrogen and mineral retention. This study focused on growth, nutrient intake and retention as its primary and secondary outcomes with no assessment on respiratory outcomes. In fact, one infant was excluded from analysis due to death from respiratory complications. The same was true for the follow up study (Brunton 1998b) in which growth, nutrient intake and retention at six and 12 months of corrected age were assessed although the results showed that the growth advantages of the experimental group at one and three months were lost by 12 months of age.

In Fewtrell 1997, infants with CLD/BPD were randomised at four to eight postnatal weeks to receive either a formula of standard energy density (24 kcal/oz) or a formula enriched with energy (30 kcal/oz), protein, carbohydrate, fat, minerals and vitamins. However, the feed volumes were reciprocally adjusted to provide the same overall nutrient and energy intakes for both groups (145 kcal/kg/day). The participants were fed the assigned formula until discharge home or until three months of corrected age. Although there was a significant difference in the total energy consumed per day between the two groups [143.3 kcal/kg/day (high-energy group) versus 130.5 kcal/kg/day (standard energy group)], the differences between two groups in the energy and protein intakes from the trial formulas failed to reach statistical significance (energy: 133.6 kcal/kg/day versus 126.7 kcal/kg/day; protein: 3.6 g/kg/day versus 3.4 g/kg/day). Neither group achieved

the predesignated energy intake of 145 kcal/kg/day as both groups were unable to feed to the targeted volumes. The standard formula group received 155.5 ml/kg (target 180 ml/kg/day). This volume of intake significantly exceeded that of the high-energy-density group (mean daily volume: 131.3 ml/kg). The mean total fluid intake of the standard formula group (combining the trial formula, expressed breast milk and intravenous fluid) was 164.7 ml/kg/day compared to the high-energy-density group with 148.3 ml/kg/day. There was no difference between the two groups in growth, respiratory outcomes, oedema and diuretic requirements.

The authors tested two main hypotheses. First, nutrient intake and growth of infants with CLD would be improved by providing nutrients in a more concentrated form. It was unclear how nutrient intake could be tested in this study, since by adjusting the targeted feed volumes according to the energy density of the assigned formulas the energy and nutrient intakes for both groups were set at identical level. The second hypothesis was that lower volume of intake would improve respiratory status. Although both groups were unable to achieve the targeted feed volumes, the mean daily volume of intake for the high-energy group was significantly lower than that of the standard-energy group. There was no difference found between the two groups in respiratory status. The failure to achieve the targeted feed volume was not attributed to feed intolerance as the formulas were well tolerated by both groups with no significant differences between the groups in the incidence of vomiting, abdominal distension and the volume of gastric aspirate. The authors suggested that the difference between the targeted and achieved volumes of intake might be explained by the subconscious reluctance of the attending staff to make up missed or incomplete feeds, or to replace gastric aspirates for fear of "fluid overload" in the high-volume group. In addition, since one-third of the infants received expressed maternal breast milk and 18% received intravenous fluid on top of their assigned formulas, it was possible that the assigned formulas were not advanced to the full targeted volumes as caregivers might have thought that breast milk and/or intravenous fluid were providing sufficient additional fluids.

Important points for future studies could be gleaned from this study. First, setting high target feed volumes to increase energy intake might not be clinically realistic for infants with CLD/BPD. Instead, to examine the effects of increased energy intake, it might be more realistic to keep the feed volume constant for both groups and vary the energy density of the trial formula. A possible fluid volume to be targeted would be 165 ml/kg/day, which was shown by this study to be potentially achievable without increased adverse effects on respiratory function or feed tolerance compared to lower fluid volumes. Second, it is important to ensure that the pre-specified volumes of the trial formulas be achieved where clinically possible, regardless of the contribution of the other sources of energy intake like breast milk or intravenous fluid.

AUTHORS' CONCLUSIONS

Implications for practice

Due to a lack of randomised control trials to date, no recommendations for practice can be made.

Implications for research

For preterm infants with or developing CLD/BPD, the optimal levels of energy intake the best methods of delivering such levels of intake and the optimal combination of various constituents of energy are important questions that remain unanswered. Research should be directed at evaluating various levels of increased (> 135 kcal/kg/day) versus standard energy intakes (98 to 135 kcal/kg/day) including the effects of increased energy density of milk feed and a combination of enteral and parenteral nutrition for this purpose. Setting high fluid volume (> 165 ml/kg/day) to achieve higher energy intake for infants with CLD/BPD might not be clinically realistic. The effects of using different nutrient supplements to boost energy intake, like carbohydrate, protein and fat, should also be examined in future studies. Assessment should also include the possible adverse effects from various methods of increasing energy intake. Target population should include all preterm infants with established or developing CLD/BPD, as defined in "type of participants" in this review. As many clinically important outcomes should be examined when studies on nutrition and CLD/BPD are designed, including short and long-term respiratory morbidities and mortality, growth and neurodevelopment. Complications that might be related to CLD/BPD like death from respiratory causes should be assessed as an outcome and not constitute grounds for exclusion.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alwaidh 1996	No comparison between different energy intake.
Atkinson 1999	Infants with CLD/BPD were excluded.
Bassiouny 2009	No comparison between different energy intake.
Brownlee 1993	No comparison between different energy intake.
Brunton 1998a	No comparison between different energy intake.
Brunton 1998b	Follow up study to Brunton 1998a. No comparison between different energy intake.
Carlson 1996	No comparison between different energy intake.
Drenckpohl 2008	This study assessed the effects of a higher starting infusion rate of intravenous fat emulsion solutions (IVFE) (2.0 grams/kg/day) versus standard rate (0.5 grams/kg/day) in VLBW infants. In all infants, the infusion rate was increased at the same rate of 0.5 grams/kg/day, until a pre-designated rate of 3.0 grams/kg/day was reached. Due to the difference in the infusion rate of IVFE, the group with the higher starting point had higher total energy intake for the first six days of the study, and reached a total energy intake of 90 kcal/kg/day sooner. This study did not aim to assess different levels of energy intake in VLBW infants. The difference in the energy intake between the two groups occurred transiently (six days), falling short of our pre-defined minimal intervention period of one month. The total energy level of 90 kcal/kg/day reached first by the group with the higher starting point during the first six days also fell short of our predefined increased energy level of at least 135 kcal/kg/day.
Fewtrell 1997	Comparison made between formula of high and standard energy densities, but feed volumes were adjusted in the study so both groups were designated to receive identical total energy intake of 145 kcal/kg/day.
Guzman 2001	Non-randomised study.
O'Connor 2003	No comparison between different energy intake.

Study	Reason for exclusion
Pereira 1994	Single group of premature infants were examined.
Sosenko 1993	No comparison between different energy intake.
Wilson 1997	No comparison between different energy intake.

APPENDICES

Appendix 1. PubMed (National Library of Medicine) Search strategy

#1: "Intensive Care, Neonatal"[Mesh]

#2: "Infant, Premature"[Mesh]

#3: "Infant, Low Birth Weight"[Mesh]

#4: #1 OR #2 OR #3

#5: "Bronchopulmonary Dysplasia"[Mesh]

#6: Bronchopulmonary dysplasia [TIAB]

#7: Chronic Lung Disease [TIAB]

#8: #5 OR #6 OR #7

#9: #4 AND #8

#10: "Parenteral Nutrition"[Mesh]

#11: "Enteral Nutrition"[Mesh]

#12: Energy [TIAB]

#13: #10 OR #11 OR #12

#14: #9 AND #13

#15: Limits: Humans, Clinical Trial, All Child: 0-18 years

Appendix 2. CENTRAL search strategy

#1: MeSH descriptor "Intensive Care, Neonatal" explode all trees
#2: Mesh descriptor "Infant, Low Birth Weight" explode all trees

#3: Mesh descriptor "Infant, Premature" explode all trees

#4: #1 OR #2 OR #3 in Clinical Trials

#5: Mesh descriptor "Bronchopulmonry dysplasia" explode all trees
#6: ("bronchopulmonary dysplasia" OR "chronic lung disease"):ti,ab,kw
#7: #5 OR #6 in Clinical Trials
#8: #4 AND #7
#9: Mesh descriptor "Parenteral Nutrition, Total" explode all trees
#10: Mesh descriptor "Enteral Nutrition" explode all trees
#11: (energy):ti,ab,kw
#12: #9 OR #10 OR #11 in Clinical Trials
#13: #8 AND #12

WHAT'S NEW

Date	Event	Description
9 May 2013	Amended	Contact author address change.

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 3, 2006

Date	Event	Description
22 January 2011	New search has been performed	This updates the review "Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease" published in the Cochrane Database of Systematic reviews (Lai 2006). Search updated in December 2010. Two potential studies were identified. Both studies were excluded. Reasons for exclusion are in the table "Characteristics of excluded studies". No change to conclusions.
5 February 2009	New search has been performed	This updates the review "Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease" published in The Cochrane Library, Issue 3, 2006 (Lai 2006). Updated search identified no new trials. No change to the conclusions of the review.
6 August 2008	Amended	Converted to RevMan 5 format. Acknowledgement list added. Search strategy revised. External source of support added.

CONTRIBUTIONS OF AUTHORS

LNM wrote the protocol.
LNM and SRAJ performed the search and identified relevant articles.
KTAN acquired full texts for articles identified to be potentially suitable.
LNM and KTAN independently assessed the eligibility of the articles identified.
LNM and KTAN wrote the description of studies, the results, discussion and conclusions.
LNM and KTAN wrote the abstract.
LNM and KTAN updated the review.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- International Medical University, Malaysia.
- McMaster University, Canada.

External sources

- SEA-ORCHID (South East Asian Optimising Reproductive and Child Health Outcomes in Developing Countries) Project, Not specified.

  Collaborative Project among four South East Asian Countries (Malaysia, Thailand, Philipines and Indonesia) with support from the Australasian Cochrane Centre

INDEX TERMS

Medical Subject Headings (MeSH)

*Energy Intake; *Infant, Premature [physiology]; Bronchopulmonary Dysplasia [*diet therapy] [physiopathology]; Child Development; Chronic Disease; Respiration

MeSH check words

Humans; Infant, Newborn