Early introduction of lipids to parenterally-fed preterm infants (Review)

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# Table of Contents

- **Header** .................................................................................................................................................. 1
- **Abstract** .................................................................................................................................................. 1
- **Plain Language Summary** ......................................................................................................................... 2
- **Background** .............................................................................................................................................. 2
- **Objectives** ................................................................................................................................................ 3
- **Methods** ................................................................................................................................................... 3
- **Results** .................................................................................................................................................... 4
- **Discussion** ................................................................................................................................................ 8
- **Authors' Conclusions** ............................................................................................................................... 8
- **Acknowledgements** ................................................................................................................................ 9
- **References** .............................................................................................................................................. 9
- **Characteristics of Studies** ......................................................................................................................... 11
- **Data and Analyses** .................................................................................................................................. 16
  - Analysis 1.1. Comparison 1 Early lipid versus no early lipids, Outcome 1 Days to regain birth weight. .......... 17
  - Analysis 1.2. Comparison 1 Early lipid versus no early lipids, Outcome 2 Rate of weight gain during period of hospital stay (g/day). ................................................................................................. 17
  - Analysis 1.4. Comparison 1 Early lipid versus no early lipids, Outcome 4 Death (irrespective of time). ........ 18
  - Analysis 1.5. Comparison 1 Early lipid versus no early lipids, Outcome 5 Neonatal death. ....................... 19
  - Analysis 1.6. Comparison 1 Early lipid versus no early lipids, Outcome 6 Chronic lung disease. ............... 19
  - Analysis 1.7. Comparison 1 Early lipid versus no early lipids, Outcome 7 Duration of respiratory support (days). ........................................................................................................................................ 20
  - Analysis 1.8. Comparison 1 Early lipid versus no early lipids, Outcome 8 Duration of supplemental oxygen (days). ................................................................................................................................. 21
  - Analysis 1.9. Comparison 1 Early lipid versus no early lipids, Outcome 9 Home oxygen. ......................... 21
  - Analysis 1.10. Comparison 1 Early lipid versus no early lipids, Outcome 10 Pneumothorax. ...................... 22
  - Analysis 1.11. Comparison 1 Early lipid versus no early lipids, Outcome 11 Pulmonary haemorrhage. ....... 22
  - Analysis 1.12. Comparison 1 Early lipid versus no early lipids, Outcome 12 Pulmonary interstitial emphysema. ........................................................................................................................................ 23
  - Analysis 1.14. Comparison 1 Early lipid versus no early lipids, Outcome 14 Necrotizing enterocolitis (any stage). ........................................................................................................................................ 23
  - Analysis 1.15. Comparison 1 Early lipid versus no early lipids, Outcome 15 Retinopathy of prematurity (any stage). ........................................................................................................................................ 24
  - Analysis 1.16. Comparison 1 Early lipid versus no early lipids, Outcome 16 Patent ductus arteriosus (clinically significant). ................................................................................................................................. 24
  - Analysis 1.18. Comparison 1 Early lipid versus no early lipids, Outcome 18 Intraventricular haemorrhage (any grade). ........................................................................................................................................ 25
  - Analysis 1.19. Comparison 1 Early lipid versus no early lipids, Outcome 19 Intraventricular haemorrhage (grade 3 and 4). ........................................................................................................................................ 26
  - Analysis 1.21. Comparison 1 Early lipid versus no early lipids, Outcome 21 Significant jaundice. ............. 26
- **What's New** ............................................................................................................................................... 26
- **History** .................................................................................................................................................... 27
- **Contributions of Authors** .......................................................................................................................... 27
- ** declarations of interest** .............................................................................................................................. 27
- **Sources of Support** .................................................................................................................................. 27
- **Index Terms** ............................................................................................................................................. 28
Early introduction of lipids to parenterally-fed preterm infants

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ABSTRACT

Background

Lipids are essential components of parenteral nutrition for preterm infants. Parenteral lipids can be administered through a peripheral vein, and their early introduction offers the potential advantages of increasing energy intake and providing essential fatty acids and fat soluble vitamins. Concerns have been raised about potential adverse effects including chronic lung disease (CLD), increase in pulmonary vascular resistance, impaired pulmonary gas diffusion, bilirubin toxicity, sepsis and free radical stress.

Objectives

To determine the safety and efficacy of 'early' (< 5 days after birth) introduction of lipids to parenterally fed preterm infants.

Search methods

Eligible studies were identified by searching MEDLINE (December 2004), EMBASE 1980 - 2004, Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2004) and CINAHL (December 1982 - December 2004). Abstracts of the Society for Pediatric Research were hand searched from 1980 to 2004 inclusive. No language restrictions were applied.

Selection criteria

All randomised or quasi randomised controlled trials comparing 'early' versus 'no early' introduction of lipids to preterm infants.

Data collection and analysis

Data were sought regarding effects on growth and risk of CLD or death, other respiratory morbidities including duration of respiratory support, duration of supplemental oxygen, the need for home oxygen, pneumothorax (PTX), pulmonary haemorrhage and pulmonary interstitial emphysema (PIE), ≥ stage 2 necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), sepsis, intraventricular haemorrhage (IVH), clinically significant thrombocytopenia and significant jaundice. Methodological quality of eligible studies was assessed according to allocation concealment, blinding of intervention, blinding of outcome assessment and completeness of follow up. When appropriate, meta-analysis was conducted to provide a pooled estimate of effect. For categorical data the Typical relative risk (RR), Typical risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals (CI) were calculated. Continuous data were analysed using weighted mean difference (WMD).
Main results

Five studies (n = 397) were included in the review. All studies compared the effectiveness and safety of 'early' introduction versus 'no early' introduction of lipids in preterm infants. The timing of introduction of 'early lipids' ranged from < 12 hours after birth to day five of life. The timing of introduction of lipids in the 'no early' lipid group ranged from day six after birth to day 14 after birth. The initial dose ranged from 0.5 - 1 g/kg/day with gradual daily increments up to a maximum of 2.5 - 3.5 g/kg/day.

For the primary outcomes (growth, death and CLD), there was no statistically significant difference between the 'early' lipid and 'no early' lipid groups.

Days to regain birth weight: [WMD 0.59 (95% CI -2.41, 3.58); two trials; N = 71].
Rate of weight gain (g/day) during period of hospital stay: [MD -2.40 (95% CI -5.30, 0.50); one trial; N = 129]
Death (irrespective of time): [Typical RR 1.04 (95% CI 0.69, 1.56); Typical RD 0.01 (95% CI -0.07, 0.08); five trials; N = 397]
Neonatal deaths: [Typical RR 1.35 (95% CI 0.78, 2.34); Typical RD 0.05 (95% CI -0.04, 0.13); four trials; N = 268].
CLD: [Typical RR 1.10 (95% CI 0.81, 1.49); Typical RD 0.04 (95% CI -0.09, 0.17); two trials; N = 193].

For the secondary outcomes of other respiratory morbidities including duration of respiratory support, duration of supplemental oxygen, PTX, pulmonary haemorrhage, PIE, NEC, ROP, PDA, sepsis, IVH and significant jaundice, there were no statistically significant differences between 'early' and 'no early' lipid groups.

Authors’ conclusions

No statistically significant effects of 'early introduction' of lipids on short term nutritional or other clinical outcomes, either benefits or adverse effects, were demonstrated in the studies reviewed. Based on the currently available evidence, 'early' initiation of lipids (≤ 5 days after birth) can not be recommended for short term growth or to prevent morbidity and mortality in preterm infants.

Plain Language Summary

Early introduction of lipids to parenterally-fed preterm infants

Premature babies who are not yet ready to digest and absorb full milk feeds are given lipids through a vein to improve their nutrition. The issue of how early the lipids should be introduced to be advantageous while causing no harm is a matter of debate. The review found that, while no side effects were reported, there was no statistically significant benefit of introducing lipids before five days of age. Long term effects of early introduction of lipids in premature babies have not been reported.

Background

Lipids are essential components of parenteral nutrition for preterm infants to provide essential fatty acids (EFA) and to meet their high energy needs. Preterm infants have very limited endogenous lipid stores (Koletzko 2002). Parenteral lipids are an attractive source of nutrition early in postnatal life because of their high energy density (Ziegler 2002), energy efficiency (Flatt 1985), isotonicity with plasma, and suitability for administration through a peripheral vein (Skeie 1988). Parenteral lipid infusion enables the delivery of fat soluble vitamins.

Even a short delay of 3-7 days in supplying lipids to parenterally fed preterm infants leads to biochemical EFA deficiency (Gutcher 1991; Friedman 1976; Foote 1991; Lee 1993). EFA deficiency increases antioxidant susceptibility in preterm infants (Tomits 2000). Prenatal and postnatal EFA deficiency reduces body and brain weights (Van Aerde 2004).

EFA deficiency can be prevented with introduction of as little as 0.5 to 1 g/kg/day lipid infusion (Cooke 1985; Gutcher 1991). Prevention of EFA deficiency in preterm infants could theoretically decrease the prevalence of complications associated with free
radical formation such as CLD and ROP (Tomsits 2000). Experimental animal studies suggest that increasing polyunsaturated fatty acids (PUFA) can confer a protective effect against the toxic effects of hyperoxia on the newborn animal lung (Sosenko 1988; Sosenko 1991).

The provision of parenteral lipids to sick preterm infants early in postnatal life may have risks. Concerns have been expressed about the potential adverse effects of 'early' lipid infusions in preterm infants including increased rates of sepsis due to coagulase negative staphylococci (Avila-Figueroa 1998), CLD and mortality (Cooke 1991). Reported pulmonary complications include deposition of fat globules in capillaries, alveolar macrophages and pulmonary arteriolar lining cells (Barson 1978; Levene 1980), interference with pulmonary gas diffusion (Greene 1976) and an increase in pulmonary vascular resistance (Prasertsom 1996). Lipid infusion in adults with adult respiratory syndrome (ARDS) causes deterioration in lung functions and haemodynamics through activation of inflammatory mediators (Lekka 2004). Some studies have shown that lipid infusions convey an increased free radical stress (Pitkanen 1991; Pitkanen 1998; Helbock 1993; Neuzil 1995). Free fatty acids released after lipolysis of the parenteral lipids may displace bilirubin from albumin binding sites, resulting in increased levels of unbound bilirubin and an increased risk of kernicterus (Spear 1985). Thrombocytopenia was reported as one of side effects of lipid infusion (Lipson 1974). Most of the current literature suggests that there is no effect of parenteral lipid infusion on platelet number or function (Spear 1990; Herson 1989).

The American Academy of Pediatrics (AAP 2003) gives recommendations about the rate of lipid infusion, but not guidelines about how early lipids can be started. Reviews on the subject recommend early initiation of lipids on the first or second day of life at a low dose of 0.5-1 g/kg/day, gradually increasing to 3-3.5 g/kg/day, and with daily infusion over 20-24 hour period (Putet 2000; Ziegler 2002; Koletzko 2002; Innis 2002; Van Aerde 2004).

A meta-analysis on the subject published in abstract form (Fox 1998 and Wilson 1998) reported that 'early' lipid infusion when compared to 'late' lipid infusion is not associated with an increased risk CLD or death. It did not address the issue of potential advantages of early lipid infusion like physical growth and reduction in incidence of free-radical-injury associated diseases of prematurity like ROP, NEC and IVH. Hence we thought it is justified to do a systematic review and meta-analysis.

OBJECTIVES

Primary objectives:
To assess the effect of 'early' (<5 days) introduction of lipids on growth and risk of CLD or death in parenterally fed preterm infants.

Secondary objectives:
To assess the effect of 'early' introduction of lipids on other respiratory morbidities including duration of respiratory support, duration of supplemental oxygen, the need for home oxygen, PTX, pulmonary haemorrhage and PIE, ≥ stage 2 NEC, ROP, PDA, sepsis, IVH, clinically significant thrombocytopenia and significant jaundice.

Subgroup analyses were planned on the basis of gestational age (<30 weeks, more than 30 weeks).

METHODS

Criteria for considering studies for this review

Types of studies
Randomised or quasi randomised controlled trials reporting at least one of the clinical outcomes.

Types of participants
Preterm infants (less than 37 weeks) who needed parenteral nutrition. Postnatal age at study entry could be ≤ 5 days.

Types of interventions
Trials comparing 'early' (<5 days) v 'no early' lipid were included. Trials comparing early versus late lipid introduction were included only if early introduction was ≤ 5 days postnatal age and late introduction was >5 days of life.
No restriction to dose of lipid infusion was applied.

Types of outcome measures
Primary
1. Physical growth: days to regain birth weight, rate of weight gain (g/kg/day) during period of hospital stay.
2. Death: before discharge and neonatal death (<28 days).
3. CLD: Oxygen therapy or any form of respiratory support at ≥28 days of life.

Secondary
1. Duration of respiratory support (days).
2. Duration of supplemental oxygen (days).
3. Need for home oxygen therapy.
4. Pneumothorax (PTX) diagnosed by transillumination or by X ray chest.
5. Pulmonary haemorrhage needing alterations in respiratory care or causing haemodynamic instability.
Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. Trials were identified by MEDLINE (1966 to December 2004), EMBASE 1980 - 2004, Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2004) and CINAHL (December 1982 - December 2004). Abstracts of the Society for Pediatric Research from 1980 to 2004 inclusive were hand searched. MEDLINE was searched using the following MeSH terms or text words: infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature AND intravenous fat emulsion, intralipid, intravenous lipid, intravenous fat, lipid infusion, parenteral lipid and lipid emulsion in different combinations. Articles so obtained were hand searched to identify randomised and quasi randomised controlled trials which addressed the issue of ‘early’ introduction of parenteral lipids to preterm infants. Reference lists of published narrative and systematic reviews were also reviewed. No language restriction was applied. The authors of all published studies were contacted to clarify reported data or provide additional information including mean and standard deviations. Soenken 1993 provided clarification of existing data, but no additional information was available. Brownlee 1993, Alwaidh 1996 (contact author Ryan) and Gilbertson 1991 (contact author Kovar) responded, but no additional information was available from these three authors. There was no response from Hammerman 1988.

Data collection and analysis

Standard methods of the Cochrane Neonatal Review Group were used.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Seven randomised control trials assessing the effect of ‘early’ introduction of lipids on various outcomes were identified.

Excluded studies

Two studies (Wilson 1997 and Ibrahim 2004) were excluded from the review because, in each study, both ‘early’ and ‘no early’ lipid groups received lipids ≤ 5 days of life.

Included studies

Five studies were included in this review. Alwaidh 1996 was a single centre study performed at Liverpool Children's Hospital, England.

• Population: Preterm infants < 1500 g birth weight who required parenteral nutrition.

• Objective: To determine whether ‘early’ introduction of lipids results in an increase in the incidence of CLD.
• Intervention: 'Early' lipid group received lipids on day five. 'No early' lipid group received lipids on day 14.
• Outcomes assessed: CLD.

Brownlee 1993 was a single centre study performed at St James’s University Hospital, Leeds, UK.
• Population: Preterm infants ≤ 1750 g birth weight, requiring IPPV at 12 hours of age, radiographic features of RDS.
• Objective: To evaluate the potential benefits and harmful effects of ‘early’ administration of lipids to preterm infants.
• Interventions: ‘Early’ lipid group received parenteral nutrition including lipids within the first 36 hours. ‘No early’ lipid group received parenteral nutrition including lipids on the sixth completed day.
• Outcomes assessed: Respiratory and nutritional.

Gilbertson 1991 was a single centre study performed at Charing Cross and Westminster Medical school, London.
• Population: Preterm infants < 1500 g birth weight, age < 6 hours, ventilator dependence, requirement for intensive medical and nursing care and estimated need for total parenteral nutrition for at least one week.
• Objective: To investigate lipid tolerance in sick, ventilator dependent, very low birth weight infants from the first day of life and the effects of ‘early’ introduction of intravenously administered lipid on glucose homeostasis and gas exchange.
• Interventions: ‘Early’ lipid group received parenteral lipids on day 1 whereas ‘no early’ lipid group received parenteral lipids on day eight.
• Outcomes evaluated: Glucose levels, glucose metabolites, blood gas values, PO2 and PCO2 as well as clinical outcomes.

Hammerman 1988 was a single centre study performed at the University of Chicago Medical Centre.
• Population: Preterm infants with birth weight < 1750 g with respiratory distress syndrome, who had not received any nutrition by day three of life and who were expected to receive parenteral nutrition for at least five subsequent days.
• Objective: 1. To evaluate the hypothesis that dietary alterations which change the concentration of EFA precursors can affect the amount of prostanooids synthesized and 2. to evaluate the clinical and haemodynamic effects of this altered prostaglandin profile on the development of various neonatal conditions that might be related to prostaglandin metabolism.
• Interventions: The ‘early’ lipid group received lipids from <12 postnatal hours and the ‘no early’ lipid group received no lipid infusion until after the seventh day.
• Outcomes evaluated: Prostaglandin metabolites and clinical outcomes.

Sosenko 1993 was a single centre study performed in the University of Miami School of Medicine, U.S.A.
• Population: Preterm infants 600 - 1000 g, requirement of mechanical ventilation at six postnatal hours for the 600 - 800 g infants, and requirement for mechanical ventilation plus supplemental oxygen at six postnatal hours for the 80 - 1000 g infants.
• Objective: To investigate whether intravenous administration of lipids within 12 hours of birth to ventilator dependent preterm infants would decrease the incidence or severity of CLD.
• Interventions: The ‘early’ lipid group received lipids from <12 postnatal hours and the ‘no early’ lipid group received no lipid infusion until after the seventh day.
• Outcomes evaluated: Clinical endpoints including mortality, CLD, ROP, other respiratory morbidities, NEC, PDA, IVH and sepsis as well as biochemical parameters (plasma and tracheal fluid fatty acid levels).

Details of the patients and the methods of five trials included in this review are summarised in the Table, “Characteristics of included studies”.

Risk of bias in included studies
The quality of the trials was assessed using the criteria of the Neonatal Review Group. Assessment was predominantly based on allocation concealment, blinding of intervention, blinding of outcome assessment and completeness of follow up.

Allocation concealment:
Allocation concealment was accomplished in Alwaidh 1996, Hammerman 1988 and Sosenko 1993 using sealed envelopes. It was not clear if allocation was concealed in Brownlee 1993. Gilbertson 1991 was quasi random (alternatively, not randomly assigned) and allocation was not concealed.

Blinding of intervention:
Sosenko 1993 and Hammerman 1988 reported that blinding of intervention was not possible because of the obvious recognizability of lipid emulsion. It is not clear whether intervention was blinded in Alwaidh 1996, Brownlee 1993. Intervention was not blinded in Gilbertson 1991.

Blinding of outcome assessment:
Only Sosenko 1993 was credited with blinding of outcome assessment. It is not clear whether outcome assessment was blinded in Hammerman 1988; Alwaidh 1996 and Brownlee 1993. It was not blinded in Gilbertson 1991.

Completeness of follow up:
Two trials (Alwaidh 1996 and Sosenko 1993) reported complete follow up. Brownlee 1993 excluded infants who died from further analysis. Gilbertson 1991 excluded data from three infants from analysis because they required TPN for less than a week. Hammerman 1988 did not have complete follow up for ROP, 11/20 in ‘early’ lipid group versus 17/22 in ‘no early’ lipid group having their eyes examined.
Effects of interventions

Five studies fulfilled our selection criteria and were included in this review (Alwaidh 1996; Brownlee 1993; Gilbertson 1991; Hammerman 1988 and Sosenko 1993). They included a total of 397 preterm infants. There was no disagreement regarding inclusion/exclusion of studies, quality assessment or data extraction. Available data were pooled and analysed as listed below. A planned subgroup analysis of preterm infants ≤ 30 weeks gestation was not possible because of lack of published data. The authors of all the studies were contacted but additional data were unavailable.

Primary outcome measures

Physical growth

a. Days to regain birth weight (01.01)

Four studies (Alwaidh 1996; Gilbertson 1991; Hammerman 1988; Sosenko 1993) involving a total of 268 preterm infants reported this outcome. No individual study found a statistically significant difference between 'early' lipid and 'no early' lipid groups. Sosenko 1993 did not report the actual data. Alwaidh 1996 reported the data as median (range) 15 (0-21) days in 'early' versus 16 (8-30) days in 'no early' lipid group. Only two studies (Gilbertson 1991; Hammerman 1988) reported the data in a form that could be pooled for meta analysis. The meta-analysis of these two studies did not support a significant effect [WMD 0.59 days (95% CI -2.40, 9.50); one trial; N = 129].

b. Rate of weight gain (g/day) during period of hospital stay (01.02)

Only Brownlee 1993 reported this outcome. There was no significant difference in daily weight gain (mean ± SD) to discharge; [MD -2.40 (95% CI -5.30, 0.50); one trial; N = 71].

Death

a. Death before discharge (01.03)

No study reported this specific outcome.

b. Death (irrespective of time) (01.04)

All five studies (Alwaidh 1996; Brownlee 1993; Gilbertson 1991; Hammerman 1988; Sosenko 1993) involving a total of 397 preterm infants reported this outcome. No individual study found a statistically significant effect of 'early' versus 'no early' lipid on this outcome. Meta analysis of all the studies did not show a significant effect of introduction of 'early' lipids on overall mortality [Typical RR 1.04 (95% CI 0.69, 1.56); Typical RD 0.01 (95% CI -0.07, 0.08); five trials; N = 397]. These are presented as post hoc findings as we did not include this outcome in our protocol.

c. Neonatal death (01.05)

Four studies involving a total of 268 preterm infants reported this outcome (Alwaidh 1996; Gilbertson 1991; Hammerman 1988; Sosenko 1993). No individual study found a statistically significant effect of 'early' versus 'no early' lipid on this outcome. Meta analysis of these four studies did not show a significant difference in the incidence of neonatal deaths between 'early' and 'no early' lipid group [Typical RR 1.35 (95% CI 0.78, 2.34); Typical RD 0.05 (95% CI -0.04, 0.13); four trials; N = 268].

Chronic lung disease (01.06)

The definition of CLD varied widely in different studies. Hammerman 1988 did not define bronchopulmonary dysplasia (BPD). They found a higher incidence of BPD in 'early' lipid versus 'no early' lipid group (14/20 versus 10/22; P < 0.10). Sosenko 1993 defined CLD as the need for supplemental oxygen for at least 28 of the first 60 days of age associated with abnormal chest X ray findings. They found no significant difference in the incidence of CLD between 'early' and 'no early' lipid group (20/70 versus 24/63 respectively). In the Gilbertson 1991 trial, diagnosis of BPD was based on history plus radiological appearance in infants requiring supplemental oxygen after 28 days of life. Only two studies (Alwaidh 1996; Brownlee 1993) involving a total of 193 preterm infants reported this outcome as per our definition (need for oxygen/respiratory support at ≥ 28 days of postnatal life). Meta-analysis of these two studies showed no significant difference in incidence of CLD between 'early' versus 'no early' lipid group [Typical RR 1.10 (95% CI 0.81, 1.49); Typical RD 0.04 (95% CI -0.09, 0.17); 2 trials; N = 193].

Secondary outcome measures

Duration of respiratory support (days) (01.07)

All the five studies (Alwaidh 1996; Brownlee 1993; Gilbertson 1991; Hammerman 1988; Sosenko 1993) involving a total of 397 preterm infants reported this outcome. Hammerman 1988 reported a statistically significant increase in the number of days of mechanical ventilation in the 'early' lipid group compared to the 'no early' lipid group (37 ± 35 versus 21 ± 18 days respectively). No other study showed a statistically significant effect of 'early' versus 'no early' lipids on this outcome. Brownlee 1996 also reported the data as median (range): 8.5 (1-45) days in 'early' versus 8 (1-95) days in 'no early' lipid group. Alwaidh 1996 also reported the data as median (range): 15 (2-91) days in 'early' versus 13 (2-60) days in 'no early' lipid group. Sosenko 1993 reported the data separately for two weight categories. In the 600-800 g category, the median duration of mechanical ventilation was 40 days in the 'early' versus 46 days in the 'no early' lipid group. In the 801-1000 g category, it was 37 days in the 'early' versus 25 days in 'no early' lipid group. Only two studies (Gilbertson 1991; Hammerman 1988) reported the data in a form that could be pooled for meta-analysis. The meta-analysis of these two studies showed no statistically significant difference between 'early' versus 'no early' lipid group [WMD 0.89 days (95% CI -8.61, 10.40; two trials; N = 71]. However caution should be exercised in interpreting this result because the analysis showed significant heterogeneity between the two studies.

Duration of supplemental oxygen (days) (01.08)

Four studies (Brownlee 1993; Gilbertson 1991; Hammerman 1988) reported this outcome.
1988; Sosenko 1993) involving 333 preterm infants reported this outcome. Only Hammerman 1988 reported a statistically significant increase in the number of days on supplemental oxygen in the ‘early’ lipid group compared to ‘no early’ lipid group (51 ± 39 versus 28 ± 23 days). Other three studies (Brownlee 1993; Gilbertson 1991; Sosenko 1993) did not find any statistically significant differences. Brownlee 1993 reported the data as median (range): 19.5 (2 - 75 days) versus 20.5 (2 - 127 days); ‘early’ versus ‘no early’ lipid respectively. Sosenko 1993 reported the data as median. No significant differences in this outcome were noted in both birth weight categories. In the 600-800 g category it was 31.5 versus 40 days (‘early’ versus ‘no early’ lipid); In the 801-1000 g category, it was 18 versus 17 days (‘early’ versus ‘no early’ lipid). Only two studies (Gilbertson 1991; Hammerman 1988) reported the data in a form that could be pooled for meta-analysis. The meta-analysis of these two studies showed no statistically significant difference between ‘early’ and ‘no early’ lipid groups [WMD 5.50 days (95% CI -8.22, 19.22); two trials; N = 71]. However caution should be exercised in interpreting this result because the analysis showed significant heterogeneity between the two studies.

**Home oxygen (01.09)**

Only one study (Hammerman 1988) reported this outcome. The need for home oxygen therapy was higher in ‘early’ lipid compared to ‘no early’ lipid group (7/20 versus 0/22). [RR 16.43 (95% CI 1.00, 270.41); RD 0.35 (95% CI 0.14, 0.56); one trial; N = 42].

**Pneumothorax (01.10)**

Only one study (Sosenko 1993) reported this outcome. There was no significant difference in the incidence of PTX between ‘early’ and ‘no early’ lipid groups [RR 0.54 (95% CI 0.21, 1.40); RD -0.07 (95% CI -0.18, 0.04); one trial; N = 133].

**Pulmonary haemorrhage (01.11)**

Only one study (Sosenko 1993) reported this outcome. In the 600-800 g category, there was a statistically significant increase in the incidence of pulmonary haemorrhage in the ‘early’ lipid versus ‘no early lipid’ group (11/42 versus 3/37). In the 801-1000 g category, there was no significant difference between ‘early’ and ‘no early’ lipid groups (6/28 versus 4/26). When the data were combined, there was a trend towards increase in pulmonary haemorrhage in ‘early’ lipid group compared to ‘no early’ lipid group which was of borderline statistical significance [RR 2.19 (95% CI 0.97, 4.92); RD 0.13 (95% CI 0.00, 0.26); one trial; N = 133].

**Pulmonary interstitial emphysema (01.12)**

Only one study (Sosenko 1993) reported this outcome. There was no significant difference in the incidence of PIE between ‘early’ versus ‘no early’ lipids [RR 0.99 (95% CI 0.45, 2.17); RD 0.00 (95% CI -0.13, 0.12); one trial; N = 133].

**Necrotizing enterocolitis (≥ stage 2) (01.13)**

None of the studies reported this outcome specifically.

**Necrotizing enterocolitis (any stage) (01.14)**

Three studies reported this outcome (Gilbertson 1991; Hammerman 1988; Sosenko 1993) and none of them showed a statistically significant difference. Meta analysis did not reveal a significant difference in the incidence of NEC between ‘early’ versus ‘no early’ lipid groups [Typical RR 0.82 (95% CI 0.34, 1.98); Typical RD -0.02 (95% CI -0.10, 0.06); three trials; N = 204]. These are presented as post hoc findings as we did not include this outcome in our protocol.

**Retinopathy of prematurity (any stage) (01.15)**

Hammerman 1988 reported an increase in the incidence of ROP (any stage) in the ‘early’ lipid group compared to ‘no early’ lipid group (8/11 v 4/17). Gilbertson 1991 and Sosenko 1993 did not show any significant difference. Meta-analysis of these three studies (Gilbertson 1991; Hammerman 1988 and Sosenko 1993) did not show a significant difference in the incidence of ROP between ‘early’ v ‘no early’ lipid groups [Typical RR 1.02 (95% CI 0.74, 1.41); Typical RD 0.01 (95% CI -0.12, 0.14); three trials; N = 204].

**Patent ductus arteriosus (clinically significant) (01.16)**

None of the studies reported on this outcome as per our definition. But four studies (Brownlee 1993; Gilbertson 1991; Hammerman 1988 and Sosenko 1993) reported on the incidence of PDA and none of them showed a statistically significant difference between the two groups. Brownlee 1993 reported that there was no significant difference between the groups regarding the incidence of PDA, but data were not given. Meta-analysis of the other three studies (Gilbertson 1991; Hammerman 1988 and Sosenko 1993) showed a trend towards decrease in the incidence of PDA in ‘early’ versus ‘no early’ lipid groups which did not reach statistical significance [Typical RR 0.84 (95% CI 0.66, 1.06); Typical RD -0.10; (95% CI -0.23, 0.03); three trials; N = 204]. These are presented as post hoc findings as we did not include this outcome in our protocol.

**Sepsis (01.17)**

None of the studies reported on the incidence of sepsis as defined in our protocol (positive blood culture). Gilbertson 1991 defined it as either blood culture positive or suggestive clinical picture with hematologic evidence indicating infection. There was no statistically significant difference in the incidence of sepsis between ‘early’ and ‘no early’ lipid groups (2/16 and 5/13 respectively). Sosenko 1993 did not define sepsis. They reported sepsis survivors (%). There were no differences between the two groups. Hammerman 1988 reported in the discussion that there was no clinical evidence of increased susceptibility to bacterial infection between the groups, but data were not given. Meta-analysis could not be performed.

**Intraventricular haemorrhage (any grade) (01.18)**

Four studies (Brownlee 1993; Gilbertson 1991; Hammerman 1988 and Sosenko 1993) involving 333 preterm infants reported this outcome. None of them showed a statistically significant difference in the incidence of IVH (any grade) between the ‘early’ and ‘no early lipid’ groups. Brownlee 1993 reported that there was no significant difference between the groups regarding the incidence of IVH, but data were not given. Meta analysis of three studies (Gilbertson 1991; Hammerman 1988 and Sosenko 1993) showed
a trend towards decrease in the incidence of IVH in the ‘early’ lipid group which did not reach statistical significance [Typical RR 0.74 (95% CI 0.53, 1.04); Typical RD -0.12 (95% CI -0.26, 0.01); three trials; N = 204].

**Intraventricular haemorrhage (Grade 3 and 4) (01.19)**

Only Hammerman 1988 involving 42 preterm infants reported this outcome and gave the actual data. There was no statistically significant difference between ‘early’ lipid and ‘no early’ lipid groups (2/20 versus 6/22 respectively) [RR 0.37 (95% CI 0.08, 1.61); RD -0.17 (95% CI -0.40, 0.06); one trial; N = 42]. Sosenko 1993 reported that there was no significant difference in the incidence of grade 3 and 4 IVH between two groups but data were not given.

**Clinically significant thrombocytopenia needing platelet transfusion (01.20)**

None of the studies reported this specific outcome. Hammerman 1988 reported no significant difference in the incidence of thrombocytopenia between ‘early’ lipid (5/20) versus ‘no early’ lipid group (6/22). The definition of thrombocytopenia was not clear. Gilbertson 1991 defined thrombocytopenia as platelet count < 150 ×10⁶. There was no significant difference between ‘early’ (5/13) and ‘no early’ lipid (7/16) groups.

**Significant jaundice (01.21)**

Only Gilbertson 1991 involving a total of 29 preterm infants reported this outcome and gave the data. Significant jaundice was defined as serum bilirubin > 200 mmol/litre (11.7 mg/dl) and requirement for phototherapy. They found no significant difference between ‘early’ v ‘no early’ lipid groups [RR 1.14 (95% CI 0.47, 2.75); RD 0.05 (95% CI -0.31, 0.41); one trial; N = 29]. Brownlee 1993 reported that there was no significant difference in the incidence of significant jaundice between the two groups, but definition and data were not given. Hammerman 1988 reported no significant difference in the bilirubin levels between ‘early’ versus ‘no early’ lipid groups on day one, three and five.

**DISCUSSION**

The outcome of ‘early’ administration of lipids on benefits and adverse effects in 397 preterm infants from five RCTs have been reported in this review. For the main outcomes of growth, death and CLD, there was no statistically significant difference between ‘early’ v ‘no early’ lipid administration. There were no significant differences in the secondary outcomes of respiratory morbidity, significant jaundice, NEC, ROP, PDA, sepsis, IVH and thrombocytopenia. An increased incidence of mortality and pulmonary haemorrhage was reported by Sosenko 1993 in the subgroup of babies with birth weight 600-800 g. However significantly fewer babies in this subgroup had received antenatal corticosteroids which may have contributed to the morbidity and mortality. Hammerman 1988 reported that ‘early’ administration of lipids to preterm infants is associated with increased incidence of CLD and ROP which was postulated as mediated by increased levels of the vasoconstrictor thromboxane B2. Similar results were not replicated by the subsequent RCTs. The meta-analysis revealed that there was a trend towards beneficial effect of ‘early’ lipid administration on the incidence of PDA and CNS haemorrhage but both did not reach statistically significant levels.

A meta-analysis (published as abstract: Fox 1998; Wilson 1998) of six prospective controlled trials in preterm infants also reported that ‘early’ lipid infusion is not associated with an increased risk of death or CLD when compared to ‘late’ lipid infusion. In addition to Alwardh 1996; Brownlee 1993; Gilbertson 1991; Hammerman 1988 and Sosenko 1993 which are included in this review, they also included Wilson 1997 in the analysis. As mentioned previously, we excluded Wilson 1997 because in both ‘early’ and ‘no early’ lipid groups, lipids were started ≤ 5 days of life. In addition to effects on death and CLD that were reported in that meta-analysis, our review compared the effect of ‘early’ versus ‘no early’ introduction of lipids on physical growth and other morbidities of prematurity.

Essential fatty acid deficiency increases antioxidant susceptibility in preterm infants (Tomsits 2000). Prevention of EFA deficiency by ‘early’ introduction of lipid emulsions could theoretically decrease the prevalence of complications associated with free radical formation such as BPD and ROP. Experimental animal studies suggest that increasing lung lipid polyunsaturated fatty acids (PUFA) can confer a protective effect against the toxic effects of hyperoxia on the newborn animal lung (Sosenko 1988; Sosenko 1991). These theoretical advantages of ‘early’ lipid administration were generally not found in clinical trials. The possible explanation may be because the morbidities of the preterm infant are multifactorial in nature rather than just related to free radical injury. Secondly the lipid emulsion itself carries an increased free radical stress (Pirkanen 1998; Helbock 1993). Elevated levels of oxidized lipids can be formed during its clinical use, especially when combined with phototherapy. Because lipid hydroperoxides are cytotoxic, inadvertent infusion of rancid lipid may add to the numerous problems encountered by preterm infants (Neuzil 1995). The apparent lack of benefit on short term physical growth may be due to the very small time difference (five days) between ‘early’ and ‘no early’ lipid as defined in this review.

Essential fatty acids are necessary for brain development (Jensen 2002). It is not clear whether a short duration of deficiency of essential fatty acids will affect long term neurodevelopmental outcomes in preterm infants. The studies in our review did not address the issue of long term neurodevelopmental outcomes.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

No statistically significant effects of ‘early’ introduction of lipids on...
short term nutritional or other clinical outcomes, either benefits or adverse effects, were demonstrated in the studies reviewed. Based on the currently available data, 'early' introduction of lipids (≤ 5 days after birth) cannot be recommended for short term growth or to prevent morbidity and mortality in preterm infants.

Implications for research
An RCT with sample size adequate to estimate effects on long term growth, respiratory and neurodevelopmental outcomes is required to determine efficacy and safety of 'early' introduction of lipids in preterm infants. Future research needs to concentrate on infants less than 28 weeks gestation as these infants have high risk of short term morbidity, mortality and long term neurodevelopmental sequelae.

Acknowledgements
We are thankful to Sosenko IRS, Brownlee KG, Ryan SW (Alwaidh 1996) and Kovar IZ (Gilbertson 1991) for responding to our queries. We are also very thankful to Tricia Scolaro, chief librarian at Princess Margaret Hospital for Children, Perth, Western Australia for her help in literature search. We are very much thankful to Jane Bell, Research Officer, Australasian Coordinating Network for the Cochrane Neonatal Review Group for her valuable suggestions in editing the review.

References to studies included in this review
Alwaidh 1996 [published data only]

Brownlee 1993 [published data only]
Brownlee KG, Kelly EJ, Ng PC, Kendall-Smith SC, Dear PR. Early or late parenteral nutrition for the sick preterm infant?. Archives of Disease in Childhood 1993;69:281–3.

Gilbertson 1991 [published data only]

Hammerman 1988 [published data only]

Sosenko 1993 [published data only]

References to studies excluded from this review
Ibrahim 2004 [published data only]

Wilson 1997 [published data only]

Additional references
AAP 2003

Avila-Figueroa 1998

Barson 1978

Bell 1978

Cooke 1985

Cooke 1991

Flatt 1985
Early introduction of lipids to parenterally-fed preterm infants (Review)

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Fox 1998

Friedman 1976

Greene 1976

Gutcher 1991

Helbock 1993

Herson 1989

ICROP 1984

Innis 2002
Innis SM. Lipid metabolism in the preterm infant. *NeoReviews* 2002; Vol. 3:e50–e51.

Jensen 2002

Koletzko 2002

Lee 1993

Lekka 2004

Levene 1980

Lipson 1974

Neuzil 1995

Papile 1978

Pitkanen 1991

Pitkanen 1998

Prasertson 1996

Putet 2000

Skeie 1988

Sosenko 1988

Sosenko 1991

Spear 1985
Spear 1990

Tomsits 2000

Van Aerde 2004

Wilson 1998

Ziegler 2002

* Indicates the major publication for the study
### Characteristics of included studies  
**[ordered by study ID]**

#### Alwaidh 1996

| Methods | Concealment of allocation- Yes (using sealed envelopes).  
Blinding of intervention- Can't tell  
Blinding of outcome assessment- Can't tell  
Completeness of follow up- Yes. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>N = 64. Infants with BW less than 1500 g who were admitted to the Intensive Care Unit and required parenteral nutrition. Exclusion criteria were not mentioned. The median (range) GA was 28 (23-31) weeks in 'early' lipid v 28 (23-31) weeks in 'no early' lipid group. Median (range) BW 997 g (536-1353) in 'early' v 1006 g (542-1486) in 'no early' lipid group</td>
</tr>
</tbody>
</table>
| Interventions | 'Early' lipid: N =32  
'No early' lipids: N =32.  
'Early lipid' group were introduced lipids on day 5. 'No early' lipid group were introduced lipids on day 14.  
Parenteral lipids as intralipid (Kabivitrium) 20% was administered in an initial dose of 0.5 g/kg/day, increasing over 5 days to 3 g/kg/day . Lipid was discontinued when >/= 50% of fluid requirements were met by milk feeds |
| Outcomes | Total days of ventilation, age at regaining BW, age at starting milk feeds, inspired ambient oxygen concentrations on day 28 and at 36 weeks post conception |
| Notes |  |

#### Brownlee 1993

| Methods | Concealment of allocation- Can't tell  
Blinding of intervention- Can't tell  
Blinding of outcome assessment- Can't tell  
Completeness of follow up- No |
|---|---|
| Participants | N = 129. Preterm infants with BW less than or equal to 1750 g still requiring IPPV at 12 hours of age with radiologic features of RDS. Infants with severe congenital anomalies or pulmonary hypoplasia were excluded.  
'Early' lipid group - median GA 29 (23 - 33), median BW 1144 g (539 -1748) .  
'No early' lipid group - median GA -29 (24 - 36), median BW 1147 g (415 -1647) |

---

*Early introduction of lipids to parenterally-fed preterm infants (Review)*

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Interventions

'Early' lipid group: N = 63.
'No early' lipid group: N = 66.
Infants randomized to the 'early' lipid group received parenteral nutrition within the first 36 hours; those in the 'no early lipid' group received parenteral nutrition on the sixth completed day. Intralipid 20% was started at a dose of 0.5 g/kg/day and increased daily by this amount to a maximum of 3.5 g/kg/day. Lipid infusions were continuous over 24 hours. Lipid intake was reduced to 1.5 g/kg/day if the serum bilirubin concentration increased to more than 200 micromols/litre, if the infant was thought to have sepsis, or if the C reactive protein was greater than 20 mg/l.

Outcomes

IPPV days, IPPV + CPAP days, oxygen therapy days, age at discharge days, weight gain at 2 weeks of age, 4 weeks of age, daily weight gain to discharge, plasma triglyceride concentrations

Notes

25 infants who died after entry into the trial were excluded from further analysis

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Gilbertson 1991

Methods

Concealment of allocation- No. Quasi randomised by alternatively assigning.
Blinding of intervention- No
Blinding of outcome assessment- No
Completeness of follow up- No

Participants

N = 29
Infants BW < 1500 g, less than 6 hours of age on admission to the NICU, ventilator dependence, requirement for intensive medical and nursing care as defined by the criteria of the British Paediatric Association, and estimated need for total parenteral nutrition for at least one week. Infants with major congenital abnormalities and infants of diabetic mothers were excluded.
The mean gestational age of infants in the 'early' lipid group was 28.60 ± 2.12 weeks and in the 'no early' lipid group was 28.80 ± 2.09 weeks. The mean birth weight of infants in the 'early' lipid group was 1150 ± 240 g and in the 'no early' lipid group was 1090 ± 324 g.

Interventions

'Early' lipid: N = 16
No early lipid: N = 13.
'Early' lipid group received TPN with lipids increasing from 1g/kg/day on the first day of life to 3 g/kg/day by day 4; 'no early' lipid group received an isocaloric, isovolumetric regimen that differed only in that it contained no lipid until eighth day and had a higher glucose concentration. Lipid was administered as intralipid 20% and infused at a constant rate over 20 hours

Outcomes

Days of ventilation, days in oxygen, maximum Fio2, maximum PIP, PaO2, PaCO2, BPD, jaundice, septicemia, thrombocytopenia, periventricular haemorrhage, NEC, PDA and ROP
Notes
Data were given as mean and SEM. SD was calculated by reviewers. The authors excluded data from 3 infants in the ‘no early’ lipid group.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>C - Inadequate</td>
</tr>
</tbody>
</table>

Hammerman 1988

Methods
Allocation concealment- Yes (using sealed envelopes).
Blinding of Intervention- No.
Blinding of outcome assessment- Can’t tell
Completeness of follow up- Can’t tell.

Participants
N = 42. Preterm infants with BW < 1750 g with RDS, who had not received any nutrition by day 3 of life and who were expected to receive parenteral nutrition for at least five subsequent days. Infants who were expected to receive enteral nutrition within the first week of life, severe jaundice or who were receiving Indomethacin were excluded.
'Early lipid' group: BW 1166 ± 431 g, GA 30 ± 3 weeks.
'No early' lipid group: BW 1086 ± 384 g, GA 29 ± 2 weeks.

Interventions
'Early lipid' group: N = 20.
'No early' lipid group: N = 22.
'Early' lipid group infants were begun on a regimen of TPN and 0.5 g/kg/day of Vitrium (lipid) concurrently; lipid infusion was increased at a rate of 0.5 g/kg/day to a maximum of 2.5 g/kg/day.
'No early' lipid group did not receive lipids until day 8.

Outcomes
Days to regain BW, PDA, IVH, NEC, bilirubin, thrombocytopenia, ROP, death, thromboxane B2 levels, AaDo2 on day 1, 3 and 5, BPD, ventilatory support (days), supplemental oxygen (days), home on oxygen (number of infants), plasma 6-keto-PGF1 alpha (day 1, 3 and 5).

Notes
It appears as though more patients had eye examinations in ‘early lipid’ group (11) compared to ‘no early’ lipid group (17). Thromboxane B2 levels were significantly elevated on day 3 and day 5 of study in the ‘early’ lipid group. This was hypothesised to be the mediator of increased respiratory morbidity and ROP in the ‘early’ lipid group.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
Methods

Allocation concealment - Yes (using sealed envelopes).
Blinding of intervention - No
Blinding of outcome assessment - Yes
Completeness of follow up - Yes

Participants

N = 133. Entry criteria - inborn infants, 600-1000 g BW, requirement of mechanical ventilation at 6 postnatal hours for the 600-800 g and requirement of mechanical ventilation plus supplemental oxygen at 6 postnatal hours for the 801-1000 g infants. Exclusion criteria - major congenital anomaly, clinical evidence of congenital infection, previability or terminal condition. Gestational age of participants was not given.

Interventions

'Early' lipid group: N = 70.
'No early' lipid group: N = 63.

Infants assigned to 'early' lipid group received 20% intralipid starting at less than 12 hours, at a dosage of 0.5 g/kg/day for the first 24 hours and then increasing 0.5 g/kg/day every 24 hours, until a dose of 1.5 g/kg was reached and was maintained through the seventh postnatal day. Lipid infusions were maintained for a 24 hour period. Infants in the 'no early' lipid group received no intralipid for until after the seventh day. The initiation of intravenous aminoacid was begun at 2 or 3 days of age in both groups.

Outcomes

Pulmonary end points - incidence of CLD, duration and quantity of oxygen exposure and mechanical ventilation for the first 2 postnatal months, mortality rate, time of death and duration of hospital stay.

Other outcome measures - PIE, PTX, pulmonary haemorrhage, PDA, NEC, ROP, sepsis.

Biochemical endpoints - fatty acids from tracheal fluid and plasma.

Notes

Most of the data were given separately for 600-800 g and 801-1000 g groups and whenever possible, data were combined. Most of the data were given as percentages. Data were extrapolated from figures and percentages when possible. Authors clarified the existing data.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim 2004</td>
<td>Both 'early' and 'no early lipid' groups received lipids within first five days after birth</td>
</tr>
<tr>
<td>Wilson 1997</td>
<td>Both 'early' and 'no early' lipid groups received lipids within first five days after birth</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. Early lipid versus no early lipids

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Days to regain birth weight</td>
<td>2</td>
<td>71</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.59 [-2.41, 3.58]</td>
</tr>
<tr>
<td>2 Rate of weight gain during period of hospital stay (g/day)</td>
<td>1</td>
<td>129</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.40 [-5.30, 0.50]</td>
</tr>
<tr>
<td>3 Death before discharge</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>4 Death (irrespective of time)</td>
<td>5</td>
<td>397</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.69, 1.56]</td>
</tr>
<tr>
<td>5 Neonatal death</td>
<td>4</td>
<td>268</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.35 [0.78, 2.34]</td>
</tr>
<tr>
<td>6 Chronic lung disease</td>
<td>2</td>
<td>193</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.10 [0.81, 1.49]</td>
</tr>
<tr>
<td>7 Duration of respiratory support (days)</td>
<td>2</td>
<td>71</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.89 [-8.61, 10.40]</td>
</tr>
<tr>
<td>8 Duration of supplemental oxygen (days)</td>
<td>2</td>
<td>71</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>5.50 [-8.22, 19.22]</td>
</tr>
<tr>
<td>9 Home oxygen</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>16.43 [1.00, 270.41]</td>
</tr>
<tr>
<td>10 Pneumothorax</td>
<td>1</td>
<td>133</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.54 [0.21, 1.40]</td>
</tr>
<tr>
<td>11 Pulmonary haemorrhage</td>
<td>1</td>
<td>133</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.19 [0.97, 4.92]</td>
</tr>
<tr>
<td>12 Pulmonary interstitial emphysema</td>
<td>1</td>
<td>133</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.99 [0.45, 2.17]</td>
</tr>
<tr>
<td>13 Necrotizing enterocolitis (&gt;/= stage 2)</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>14 Necrotizing enterocolitis (any stage)</td>
<td>3</td>
<td>204</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.82 [0.34, 1.98]</td>
</tr>
<tr>
<td>15 Retinopathy of prematurity (any stage)</td>
<td>3</td>
<td>204</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.02 [0.74, 1.41]</td>
</tr>
<tr>
<td>16 Patent ductus arteriosus (clinically significant)</td>
<td>3</td>
<td>204</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.84 [0.66, 1.06]</td>
</tr>
<tr>
<td>17 Sepsis</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>18 Intraventricular haemorrhage (any grade)</td>
<td>3</td>
<td>204</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.74 [0.53, 1.04]</td>
</tr>
<tr>
<td>19 Intraventricular haemorrhage (grade 3 and 4)</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.37 [0.08, 1.61]</td>
</tr>
<tr>
<td>20 Clinically significant thrombocytopenia needing platelet transfusion</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>21 Significant jaundice</td>
<td>1</td>
<td>29</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.47, 2.75]</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 Early lipid versus no early lipids, Outcome 1 Days to regain birth weight.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 1 Days to regain birth weight

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Gilbertson 1991</td>
<td>16</td>
<td>10.1 (5.32)</td>
<td>13</td>
<td>11.4 (6.92)</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>20</td>
<td>19 (7)</td>
<td>22</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>36</td>
<td>35</td>
<td>100.0 %</td>
<td>0.59 [-2.41, 3.58]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 1.14, df = 1 (P = 0.29); I$^2$ = 12%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Early lipid versus no early lipids, Outcome 2 Rate of weight gain during period of hospital stay (g/day).

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 2 Rate of weight gain during period of hospital stay (g/day)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>early lipid</th>
<th>no early lipid</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Brownlee 1993</td>
<td>63</td>
<td>18.6 (7.7)</td>
<td>66</td>
<td>21 (9.1)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>66</td>
<td>100.0 %</td>
<td>-2.40 [-5.30, 0.50]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Not applicable
### Analysis 1.4. Comparison Early lipid versus no early lipids, Outcome 4 Death (irrespective of time).

**Review:** Early introduction of lipids to parenterally-fed preterm infants

**Comparison:** Early lipid versus no early lipids

**Outcome:** 4 Death (irrespective of time)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>No early lipid n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwaidh 1996</td>
<td>1/32</td>
<td>1/32</td>
<td>2.8 % 1.00 [0.07, 15.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brownlee 1993</td>
<td>11/63</td>
<td>14/66</td>
<td>38.4 % 0.82 [0.40, 1.67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilbertson 1991</td>
<td>1/16</td>
<td>2/13</td>
<td>6.2 % 0.41 [0.04, 4.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>2/20</td>
<td>2/22</td>
<td>5.3 % 1.10 [0.17, 7.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>23/70</td>
<td>16/63</td>
<td>47.3 % 1.29 [0.75, 2.22]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>201</strong></td>
<td><strong>196</strong></td>
<td>100.0 % 1.04 [0.69, 1.56]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 38 (Early lipid), 35 (No early lipid)

Heterogeneity: Chi² = 1.70, df = 4 (P = 0.79); I² = 0.0%

Test for overall effect: Z = 0.19 (P = 0.85)
### Analysis 1.5. Comparison 1 Early lipid versus no early lipids, Outcome 5 Neonatal death.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 5 Neonatal death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwaidh 1996</td>
<td>1/32</td>
<td>1/32</td>
<td>5.6 % 1.00 [ 0.07, 15.30 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilbertson 1991</td>
<td>1/16</td>
<td>2/13</td>
<td>12.4 % 0.41 [ 0.04, 4.00 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>2/20</td>
<td>2/22</td>
<td>10.7 % 1.10 [ 0.17, 7.09 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>21/70</td>
<td>12/63</td>
<td>71.2 % 1.58 [ 0.85, 2.93 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>138</strong></td>
<td><strong>130</strong></td>
<td><strong>100.0 %</strong> 1.35 [ 0.78, 2.34 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 25 (early lipid), 17 (no early lipid)

Heterogeneity: Chi$^2 = 1.39$, df = 3 ($P = 0.71$); $I^2 = 0.0$

Test for overall effect: Z = 1.06 ($P = 0.29$)

---

### Analysis 1.6. Comparison 1 Early lipid versus no early lipids, Outcome 6 Chronic lung disease.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 6 Chronic lung disease

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwaidh 1996</td>
<td>23/32</td>
<td>20/32</td>
<td>50.6 % 1.15 [ 0.81, 1.62 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brownlee 1993</td>
<td>20/63</td>
<td>20/66</td>
<td>49.4 % 1.05 [ 0.63, 1.75 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>95</strong></td>
<td><strong>98</strong></td>
<td><strong>100.0 %</strong> 1.10 [ 0.81, 1.49 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 43 (Early lipid), 40 (no early lipid)

Heterogeneity: Chi$^2 = 0.10$, df = 1 ($P = 0.75$); $I^2 = 0.0$

Test for overall effect: Z = 0.61 ($P = 0.54$)
**Analysis 1.7. Comparison 1 Early lipid versus no early lipids, Outcome 7 Duration of respiratory support (days).**

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 7 Duration of respiratory support (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>16</td>
<td>13</td>
<td>69.0 %</td>
<td>-5.88</td>
<td>[ -17.32, 5.56 ]</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>20</td>
<td>22</td>
<td>31.0 %</td>
<td>16.00</td>
<td>[ -1.08, 33.08 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>36</strong></td>
<td><strong>35</strong></td>
<td>100.0 %</td>
<td>0.89</td>
<td>[ -8.61, 10.40 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.35, df = 1 (P = 0.04); I² = 77%

Test for overall effect: Z = 0.18 (P = 0.85)

Test for subgroup differences: Not applicable
Analysis 1.8. Comparison 1 Early lipid versus no early lipids, Outcome 8 Duration of supplemental oxygen (days).

Review: Early introduction of lipids to parenterally-fed preterm infants
Comparison: 1 Early lipid versus no early lipids
Outcome: 8 Duration of supplemental oxygen (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>16</td>
<td>13</td>
<td>-5.70 [-23.27, 11.87]</td>
<td>61.0 %</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>20</td>
<td>22</td>
<td>23.00 [1.04, 44.96]</td>
<td>39.0 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>36</td>
<td>35</td>
<td>5.50 [-8.22, 19.22]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.00, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Early lipid versus no early lipids, Outcome 9 Home oxygen.

Review: Early introduction of lipids to parenterally-fed preterm infants
Comparison: 1 Early lipid versus no early lipids
Outcome: 9 Home oxygen

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammerman 1988</td>
<td>7/20</td>
<td>0/22</td>
<td>16.43 [1.00, 270.41]</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>22</td>
<td>16.43 [1.00, 270.41]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total events: 7 (Early lipid), 0 (no early lipid)
Heterogeneity: not applicable
Test for overall effect: Z = 1.96 (P = 0.050)
### Analysis 1.10. Comparison 1 Early lipid versus no early lipids, Outcome 10 Pneumothorax.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 10 Pneumothorax

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sosenko 1993</td>
<td>6/70</td>
<td>10/63</td>
<td></td>
<td>100.0%</td>
<td>0.54 [0.21, 1.40]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>70</strong></td>
<td><strong>63</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.54 [0.21, 1.40]</strong></td>
</tr>
</tbody>
</table>

Total events: 6 (Early lipid), 10 (no early lipid)

Heterogeneity: not applicable

Test for overall effect: Z = 1.27 (P = 0.21)

---

### Analysis 1.11. Comparison 1 Early lipid versus no early lipids, Outcome 11 Pulmonary haemorrhage.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 11 Pulmonary haemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sosenko 1993</td>
<td>17/70</td>
<td>7/63</td>
<td></td>
<td>100.0%</td>
<td>2.19 [0.97, 4.92]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>70</strong></td>
<td><strong>63</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.19 [0.97, 4.92]</strong></td>
</tr>
</tbody>
</table>

Total events: 17 (Early lipid), 7 (no early lipid)

Heterogeneity: not applicable

Test for overall effect: Z = 1.89 (P = 0.059)
### Analysis 1.12. Comparison 1 Early lipid versus no early lipids, Outcome 12 Pulmonary interstitial emphysema.

**Review:** Early introduction of lipids to parenterally-fed preterm infants  
**Comparison:** 1 Early lipid versus no early lipids  
**Outcome:** 12 Pulmonary interstitial emphysema

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sosenko 1993</td>
<td>11/70</td>
<td>10/63</td>
<td>0.99 [0.45, 2.17]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>70</strong></td>
<td><strong>63</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.99 [0.45, 2.17]</strong></td>
</tr>
</tbody>
</table>

Total events: 11 (Early lipid), 10 (no early lipid)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.03 (P = 0.98)

### Analysis 1.14. Comparison 1 Early lipid versus no early lipids, Outcome 14 Necrotizing enterocolitis (any stage).

**Review:** Early introduction of lipids to parenterally-fed preterm infants  
**Comparison:** 1 Early lipid versus no early lipids  
**Outcome:** 14 Necrotizing enterocolitis (any stage)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>1/16</td>
<td>1/13</td>
<td>11.0% 0.81 [0.06, 11.77]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>2/20</td>
<td>0/22</td>
<td>4.8% 5.48 [0.28, 107.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>5/70</td>
<td>8/63</td>
<td>84.2% 0.56 [0.19, 1.63]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>106</strong></td>
<td><strong>98</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.82 [0.34, 1.98]</strong></td>
</tr>
</tbody>
</table>

Total events: 8 (Early lipid), 9 (no early lipid)  
Heterogeneity: Chi² = 2.05, df = 2 (P = 0.36); I² = 2%  
Test for overall effect: Z = 0.43 (P = 0.67)
Analysis 1.15. Comparison 1 Early lipid versus no early lipids, Outcome 15 Retinopathy of prematurity (any stage).

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 15 Retinopathy of prematurity (any stage)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>0/16</td>
<td>1/13</td>
<td></td>
<td>4.1 %</td>
<td>0.27 [ 0.01, 6.23 ]</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>8/20</td>
<td>4/22</td>
<td></td>
<td>9.5 %</td>
<td>2.20 [ 0.78, 6.20 ]</td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>34/70</td>
<td>33/63</td>
<td></td>
<td>86.4 %</td>
<td>0.93 [ 0.66, 1.30 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 106 98 100.0 % 1.02 [ 0.74, 1.41 ]

Total events: 42 (Early lipid), 38 (no early lipid)
Heterogeneity: Chi² = 3.10, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.13 (P = 0.90)

Analysis 1.16. Comparison 1 Early lipid versus no early lipids, Outcome 16 Patent ductus arteriosus (clinically significant).

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 16 Patent ductus arteriosus (clinically significant)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>no early lipid</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>4/16</td>
<td>6/13</td>
<td></td>
<td>10.7 %</td>
<td>0.54 [ 0.19, 1.52 ]</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>7/20</td>
<td>7/22</td>
<td></td>
<td>10.8 %</td>
<td>1.10 [ 0.47, 2.59 ]</td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>43/70</td>
<td>46/63</td>
<td></td>
<td>78.5 %</td>
<td>0.84 [ 0.66, 1.07 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 106 98 100.0 % 0.84 [ 0.66, 1.06 ]

Total events: 54 (Early lipid), 59 (no early lipid)
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0.0%
Test for overall effect: Z = 1.49 (P = 0.14)
### Analysis 1.18. Comparison 1 Early lipid versus no early lipids, Outcome 18 Intraventricular haemorrhage (any grade).

**Review:** Early introduction of lipids to parenterally-fed preterm infants  
**Comparison:** 1 Early lipid versus no early lipids  
**Outcome:** 18 Intraventricular haemorrhage (any grade)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid n/N</th>
<th>no early lipid n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>5/16</td>
<td>7/13</td>
<td></td>
<td>16.1 %</td>
<td>0.58 [0.24, 1.40]</td>
</tr>
<tr>
<td>Hammerman 1988</td>
<td>7/20</td>
<td>9/22</td>
<td></td>
<td>17.9 %</td>
<td>0.86 [0.39, 1.87]</td>
</tr>
<tr>
<td>Sosenko 1993</td>
<td>25/70</td>
<td>30/63</td>
<td></td>
<td>66.0 %</td>
<td>0.75 [0.50, 1.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>106</td>
<td>98</td>
<td></td>
<td>100.0 %</td>
<td>0.74 [0.53, 1.04]</td>
</tr>
</tbody>
</table>

Total events: 37 (Early lipid), 46 (no early lipid)  
Heterogeneity: Chi$^2 = 0.43$, df = 2 ($P = 0.81$); $I^2 = 0.0$

Test for overall effect: $Z = 1.76$ ($P = 0.079$)
### Analysis 1.19. Comparison 1 Early lipid versus no early lipids, Outcome 19 Intraventricular haemorrhage (grade 3 and 4).

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 19 Intraventricular haemorrhage (grade 3 and 4)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>No early lipid</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammerman 1988</td>
<td>2/20</td>
<td>6/22</td>
<td>100.0 %</td>
<td>0.37 [0.08, 1.61]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 20 22 100.0 % 0.37 [0.08, 1.61]

Total events: 2 (early lipid), 6 (no early lipid)
Heterogeneity: not applicable
Test for overall effect: Z = 1.33 (P = 0.18)

### Analysis 1.21. Comparison 1 Early lipid versus no early lipids, Outcome 21 Significant jaundice.

Review: Early introduction of lipids to parenterally-fed preterm infants

Comparison: 1 Early lipid versus no early lipids

Outcome: 21 Significant jaundice

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early lipid</th>
<th>No early lipid</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 1991</td>
<td>7/16</td>
<td>5/13</td>
<td>100.0 %</td>
<td>1.14 [0.47, 2.75]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 16 13 100.0 % 1.14 [0.47, 2.75]

Total events: 7 (Early lipid), 5 (no early lipid)
Heterogeneity: not applicable
Test for overall effect: Z = 0.29 (P = 0.78)
**WHAT'S NEW**
Last assessed as up-to-date: 20 February 2005.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>16 October 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
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**HISTORY**
Protocol first published: Issue 1, 2005
Review first published: Issue 2, 2005

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>21 February 2005</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**
Karen Simmer framed the questions for the protocol, performed literature search, selected relevant studies, assessed the methodological quality of studies, checked the data entered into RevMan by Shripada Rao, revised the drafts of the protocol and the review, provided guidance in selecting outcomes of interest, and revised the discussion and conclusions.

Shripada Rao wrote the protocol, performed literature search and selected relevant studies, assessed the methodological quality of the studies, extracted study data, entered the data into RevMan, corresponded with authors of the studies to get additional information, wrote the review and compiled other references.

**DECLARATIONS OF INTEREST**
None

**SOURCES OF SUPPORT**

**Internal sources**
- King Edward Memorial Hospital for Women, Perth, Western Australia, Australia.
External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Premature; *Parenteral Nutrition; Fatty Acids, Essential [deficiency]; Infant, Newborn; Infant, Premature, Diseases [etiology]; Lipids [*administration & dosage; adverse effects]; Lung Diseases [etiology]; Time Factors

MeSH check words

Humans