Commentary on “Lipid Emulsions for Parenterally Fed Preterm Infants”

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Commentary

Lipid emulsions provide essential fatty acids and lipid soluble vitamins, as well as a substantial fraction of the non-protein energy content of parenteral nutrition for supporting preterm or sick newborn infants. Traditional soybean oil-based emulsions, however, contain few medium-chain triglycerides and insufficient levels of omega-3 long-chain polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid to meet recommended needs. Consequently, soybean oil-based emulsions are thought to have low antioxidant capacity, and use has been associated with adverse effects attributed to oxidative stress, lipid peroxidation, and inflammation. A common clinical concern is that prolonged administration of soybean oil-based emulsions contributes to the pathogenesis of cholestatic “parenteral nutrition-associated liver disease” (PNALD) that can progress to hepatic steatosis, fibrosis, and liver failure [1].

Newer multi-component (composite) lipid emulsion formulations containing additional olive, coconut, or fish oils (a rich source of omega-3 fatty acids) have been developed to obviate these nutritional and metabolic problems [2]. A 2018 European expert group consensus guideline recommends considering the use of composite lipid emulsions (with or without fish oil) rather than soybean oil-based emulsions as the preferred option for prevent-

ing PNALD in newborn infants receiving parenteral nutrition for more than a few days [3].

The evidence base for this practice has been appraised and synthesized in the recently updated Cochrane review of randomized controlled trials of different lipid emulsions for parenterally fed preterm infants [4]. The authors identified 29 eligible trials, but these were generally small (2,037 infants participating in total), had methodological weaknesses (including incomplete assessment and selective reporting of outcome data), and some heterogeneity in the definition of PNALD.

Meta-analysis did not show an effect of composite lipid emulsion without fish oil- versus soybean oil-based emulsion on the risk of developing PNALD (either when defined as serum conjugated bilirubin >2 mg/dL or as per the primary investigators’ definition). Meta-analyses of trials of fish oil-containing emulsion versus soybean oil-based emulsion did not show an effect on PNALD (serum conjugated bilirubin >2 mg/dL). There was some evidence that use of fish oil-containing emulsions reduced the risk of PNALD (as per primary investigators’ definitions), but a sensitivity analysis excluding a trial at high risk of bias did not show an effect (Fig. 1 [5–14]).

The review did not show any evidence of an effect of fish oil-containing lipid emulsions on other outcomes, including bronchopulmonary dysplasia and retinopathy of prematurity, that might plausibly be affected by the

Fig. 1. Effect of fish oil-containing lipid emulsion versus lipid emulsion without fish oil on PNALD (investigators' definition).

anti-oxidative effects of omega-3 long-chain polyunsaturated fatty acids in fish oil. These findings are consistent with those of a recent large randomized controlled trial that showed that enteral supplementation with lipid emulsion-containing docosahexaenoic acid did not confer any benefits, including any effect on bronchopulmonary dysplasia, for infants born before 29 weeks' gestation [15].

Using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods [16], the authors assessed the evidence for the effects of composite lipid emulsion (with or without fish oil) on PNALD as "low" because of risk of bias in the included trials and the imprecision of estimates of effect (95% confidence interval included harmful or beneficial effect estimates). The review concluded that given this paucity of evidence for superiority of 1 lipid emulsion versus another to prevent PNALD in preterm or sick newborn infants, there is justification for undertaking further high-quality trials to provide data of sufficient validity and applicability to inform policy and practice.

Acknowledgements

Cochrane Neonatal reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Source

National Institute of Health Research (UK) Cochrane Programme Grant (16/114/03).

Author Contributions

All authors contributed to writing this commentary.

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Cochrane Abstract

Background: Conventionally used soybean oil-based lipid emulsions (S-LE) have high polyunsaturated fatty acid content and phytosterols that may contribute to adverse effects in preterm infants. The newer lipid emulsions (LE) from different lipid sources are currently available for use in preterm infants. **Objectives:** The aim of this study was to compare the safety and efficacy of all LE for parenteral nutrition (PN) in preterm infants (less than 37 weeks' gestation) including preterm infants with surgical conditions or parenteral nutrition-associated liver disease (PNALD)/cholestasis using direct comparisons and pair-wise meta-analyses. **Search Methods:** We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 5), MEDLINE (1946 to June 18, 2018), Embase (1974 to July 18, 2018), CINAHL (1982 to June 18, 2018), MIDRIS (1971 to May 31, 2018), conference proceedings, trial registries (ClinicalTrials.gov and WHO's Trials Registry and Platform), and reference lists of retrieved articles. **Selection Criteria:** Randomized or quasi-randomized controlled studies in preterm infants with or without surgical conditions or PNALD within the first 6 months of life. **Data Collection and Analysis:** Data collection and analysis conformed to the methods of Cochrane Neonatal. We used the

GRADE approach to assess the quality of evidence for important outcomes in addition to reporting statistical significance of results. **Main Results:** We included 29 studies ($n = 2,037$) in this review. Lipid emulsions (LE) were classified in 3 broad groups: (1) all fish oil-containing LE including pure fish oil-LE (F-LE) and multisource LE (e.g., medium-chain triglycerides (MCT)-olive-fish-soybean oil-LE (MOFS-LE), MCT-fish-soybean oil-LE (MFS-LE), and olive-fish-soybean oil-LE (OFS-LE); (2) conventional S-LE; (3) alternative LE (e.g., MCT-soybean oil-LE (MS-LE), olive-soybean oil LE, and borage oil-based LE). We considered the following broad comparisons: fish oil LE versus non-fish oil LE, fish oil LE versus another fish oil LE, alternative LE versus S-LE; alternative LE versus another alternative LE in preterm infants less than 37 weeks' gestation, preterm infants with surgical conditions, and preterm infants with parenteral nutrition-associated liver disease (PNALD)/cholestasis. Separate subgroup comparisons of each LE preparation were included within these broader groups. Most studies in preterm infants used PN for mean duration of 4 weeks or less and for longer duration in infants with cholestasis or surgical conditions. We defined the primary outcome of PNALD/cholestasis as conjugated bilirubin (Cbil) 2 mg/dL or greater and resolution of PNALD/cholestasis as Cbil less

than 2 mg/dL. There was heterogeneity in definitions used by the included studies with Cbil cut-offs ranging from 17.1 μ mol/L (1 mg/dL) up to 50 μ mol/L (about 3 mg/dL). In preterm infants, meta-analysis found no evidence of a difference in the incidence of PNALD/cholestasis (Cbil cut-off: 2 mg/dL) between fish oil-LEs and all non-fish oil LEs (typical risk ratio (RR) 0.61, 95% confidence interval (CI) 0.24–1.56; typical risk difference (RD) –0.03, 95% CI –0.08 to 0.02; 4 studies; n = 328; low-quality evidence). We also considered an outcome allowing for any definition of PNALD (different Cbil cut-offs). In the meta-analysis for PNALD/cholestasis, using any definition and restricted to low or unclear risk of bias studies, there was no evidence of a difference between fish oil LE and all non-fish oil LE for incidence of cholestasis (typical RR 0.80, 95% CI 0.53–1.21; typical RD –0.02, 95% CI –0.05 to 0.02; 10 studies; n = 1024; low-quality evidence). There was no evidence of difference in subgroup meta-analyses of individual LE types in any comparison. In preterm infants with surgical conditions or cholestasis, there was only 1 small study each reporting no evidence of a difference in incidence or resolution of cholestasis respectively with use of a pure F-LE versus S-LE (using a Cbil cut-off of 2 mg/dL). In preterm infants with PNALD/cholestasis (using any definition), the meta-analysis showed significantly less cholestasis with the use of fish oil-LE compared to S-LE (typical RR 0.54, 95% CI 0.32–0.91; typical RD –0.39, 95% CI –0.65 to –0.12; number needed to treat for an additional beneficial outcome 3, 95% CI 2–9; 2 studies; n = 40; very low-quality evidence). However, this outcome had a very low number of participants from 2 small studies with methodological differences, one of which was terminated early, increasing the uncertainty about effect estimates. There were no differences between LE types in pair-wise meta-analyses for growth in preterm infants. There was paucity

of studies in preterm infants with surgical conditions or cholestasis to perform meta-analyses for growth and most other outcomes. In the secondary outcomes for preterm infants, there was no difference between fish-oil LE and non-fish oil LE in meta-analysis for severe retinopathy of prematurity (ROP) (stage 3 or greater, or requiring surgery: typical RR 0.80, 95% CI 0.55–1.16; typical RD –0.03, 95% CI –0.07 to 0.02; 7 studies; n = 731; very low-quality evidence). There were no differences in the LE types in pair-wise meta-analyses for death, bronchopulmonary dysplasia, ventilation duration, patent ductus arteriosus, sepsis, necrotizing enterocolitis, intraventricular haemorrhage, periventricular leukomalacia, jaundice, hyperglycaemia, hypertriglyceridaemia, intrahepatic lipid content, and conjugated bilirubin levels in any comparison. In surgical infants, 1 study (n = 19) reported no differences in death, sepsis rates, Cbil, and neurodevelopmental outcomes with pure F-LE versus S-LE. In infants with cholestasis, there were no evidence of differences in death or sepsis in meta-analyses between fish oil-LE and S-LE (2 studies; n = 40; very low-quality evidence). **Reviewer's Conclusions:** In the current review, we did not find any particular LE with or without fish oil to be better than another LE in preterm infants for prevention of PNALD/cholestasis, growth, mortality, ROP, bronchopulmonary dysplasia, and other neonatal outcomes. In preterm infants with surgical conditions or cholestasis, there is currently insufficient evidence from randomized studies to determine with any certainty if fish oil LEs offer advantage in prevention or resolution of cholestasis or in any other clinical outcome. Further research, with larger well-designed trials, is warranted to evaluate the ideal composition of LE in preterm infants and the role of fish oil-containing and other LEs in the prevention and resolution of PNALD, ROP, and other clinical outcomes.