Clinical Nutrition ESPEN xxx (2017) e1–e7

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Randomized Controlled Trial

Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial

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ARTICLE INFO

Article history:
Received 3 April 2017
Accepted 12 April 2017

Keywords:
Preterm
Parenteral nutrition
Long-chain polyunsaturated fatty acids
Morbidities
Growth

SUMMARY

Background & aims: The purpose of the study was to compare the effects of the parenteral emulsion SMOFlipid®, with 15% fish oil, with Clinoleic® on retinopathy of prematurity (ROP) and other morbidities and growth, and to compare their impact on longitudinal serum levels of fatty acids. Retinopathy of prematurity, other morbidity and growth were correlated with each parenteral lipid supplement.

Methods: Ninety infants born at gestational age <28 weeks were randomized to treatment with SMOFlipid® or Clinoleic®. Two thirds (66%) of the infants received parenteral nutrition for up to 14 days birth (median 8, range 2–14 days), and additional 25% of the infants received for up to 28 days after birth (median 21, range 15–28 days). Cord blood samples and then venous blood samples were obtained at ages 1, 7, 14, and 28 days and at postmenstrual age (PMA) 32, 36, and 40 weeks. Breastmilk was collected at postnatal day 7, and at PMA 32 and 40 weeks. Serum phospholipid and breastmilk total fatty acids were analyzed by gas chromatography–mass spectrometry. Treatment groups were compared with regard to ROP, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus sepsis and growth between birth and 36 weeks.

Results: Infants on SMOFlipid® had higher fractions of omega-3 LCPUFA eicosapentaenoic acid (EPA) and slightly higher omega-3 LCPUFA docosahexaenoic acid (DHA) fraction and a decreased arachidonic acid (AA) to DHA ratio from one week after birth up to 32 postmenstrual weeks compared to infants on Clinoleic®. Treatment groups did not differ in morbidities or growth.

Conclusion: Supplementation with SMOFlipid® containing 15% fish oil during parenteral nutrition increased EPA substantially, DHA marginally, reduced AA and decreased AA to DHA ratio. It did not reduce morbidity or affect growth. Since extremely preterm infants accumulate a large deficit of DHA and AA, studies on more prolonged or different levels of DHA and AA supplementation are warranted.

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http://dx.doi.org/10.1016/j.clnesp.2017.04.004

Key notes

Parenteral nutrition with a lipid solution containing omega-3 long chain polyunsaturated fatty acids in fish oil (SMOFlipid®) compared to an olive oil based solution (Clinoleic®) to extremely preterm infants increased the serum fraction of EPA substantially and that of DHA marginally, and decreased that of AA as well as of AA/DHA ratio. Morbidities and growth were not affected.

Clinical Relevancy Statement

Long chain polyunsaturated fatty acids (LCPUFAs) are essential for normal structural and functional development of the fetus, especially the retina and CNS. These fatty acids are lacking in commonly used lipid solutions for parenteral use in preterm infants. The resultant deficiency is thought to contribute to prematurity related morbidities. Newer lipid solutions provide LCPUFAs derived from fish oil. Compared to olive oil based Clinoleic® SMOFlipid® containing 15% fish oil did not affect morbidities or growth but resulted in significant changes in longitudinal serum fatty acid composition and a decreased arachidonic to docosahexaenoic acid ratio. Alternative strategies to provide LCPUFAs to the preterm infant need to be investigated.

1. Introduction

Extremely preterm infants are at increased risk of poor growth and development and prone to develop morbidities and dysfunctions both short and long term. These infants miss the third trimester of gestation *in utero* and the supply of nutrients, hormones, and other factors that are normally provided in amounts appropriate for developmental stage. Instead, they rely on parenteral nutrition for the first weeks after birth with lipid solutions lacking important components. During gestation, long-chain polyunsaturated fatty acids (LCPUFAs), which are structural constituents of most cell membranes, and play functional roles in fetal development, are selectively transferred from the mother to the fetus [1,2]. The omega-3 LCPUFA docosahexaenoic acid (DHA) is an important component in cell membranes in the CNS including the retina. In addition, omega-3 LCPUFAs influence the immune response and are precursors of resolvins and protectins which promote resolution of inflammation [3]. Dietary DHA is mainly derived from oily fish, which in turn obtain the LCPUFAs from microalgae [4]. Preterm infants can synthesize small amounts DHA [5] but not enough to meet their developmental needs. During the third trimester, 80% of fetal brain DHA accumulates, and large amounts are accumulated in adipose tissue [6]. Very preterm infants develop a large deficit in DHA as well as in the omega-6 LCPUFA arachidonic acid (AA) during parenteral nutrition with commonly used soybean- [7] and olive oil-based lipid emulsions [8] as well as during enteral nutrition even with breastfeeding [9,10]. Lapillonne et al. have estimated that an infant born at gestational age (GA) 27 weeks weighing 1000 g will have a DHA deficit of 600 mg/kg at age 4 weeks [11] which is thought to contribute to preterm morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and white matter injury and sepsis [12]. Supplementation of omega-3 LCPUFA to preterm children was recently reviewed by Zhang et al. [13]. No randomized controlled trials had targeted a population with exclusively extremely preterm infants (born at a GA <28 weeks). In a systematic review of omega-3 supplementation to infants born at GA ≤32 weeks a reduction in the incidence of NEC and a trend of decreased risk of BPD was found [13]. Dietary omega-3 LCPUFAs reduces pathologic retinal neovascularization in oxygen-induced retinopathy in mice [14–17]. With regard to ROP, studies of fish oil supplementation have reported a reduction in the need for laser therapy [18,19], less ROP but no difference in the need for treatment [20] as well as no benefit [21,22].

The most immature infants develop the largest DHA deficit and are most likely to benefit from supplementation [23]. The aims of this study were to determine and compare serum LCPUFA (DHA, eicosapentaenoic acid (EPA) and AA) profiles, ROP, BPD, NEC, patent ductus arteriosus (PDA), sepsis and growth in extremely preterm infants receiving parenteral nutrition with an olive oil-based lipid solution (Clinoleic®, Baxter) or a solution containing 15% fish oil with omega-3 LCPUFAs (SMOFlipid®, Fresenius Kabi).

2. Patients and methods

Included were infants with GA <28 weeks admitted to the neonatal intensive care unit at Sahlgrenska University Hospital in Gothenburg, Sweden, from 04/04/13 to 09/22/15. Exclusion criteria were major congenital malformations. Of the 138 infants born at GA <28 weeks during this period, parents of 90 eligible infants agreed to participation after informed consent (Fig. 1, Table 1). Randomization was in blocks of 20 infants, adjusting for GA to ensure equal numbers of Clinoleic®- and SMOFlipid®-treated infants in each GA group. Twins were randomized to the same lipid solution due to ethical concerns. The treating nurse/doctor received the randomization online. Type of lipid emulsion was blinded for data analysis and the screening ophthalmologists.

2.1. Routine nutritional management

2.1.1. Nutritional strategy

The nutritional strategy has been described previously [24]. Briefly, parenteral nutrition was initiated as soon as possible after birth with a standard solution containing Vaminolac and 10% Glucose (total protein content 2 g/100 mL) aiming at 80–90 mL/kg/

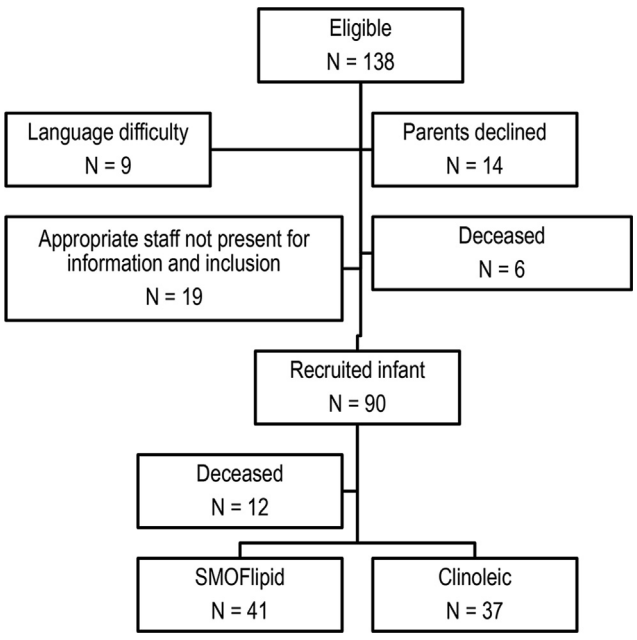

Fig. 1. Patient enrollment flow chart.

Please cite this article in press as: Najm S, et al., Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial, Clinical Nutrition ESPEN (2017), http://dx.doi.org/10.1016/j.clnesp.2017.04.004