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The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: A randomized controlled trial ☆

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ABSTRACT

Objective: To compare the effect of two lipid emulsions on the development of retinopathy of prematurity in very low birth weight infants.
Design: Randomized controlled study.
Patients and methods: Eighty very low birth weight infants receiving parenteral nutrition from the first day of life were evaluated. One of the two lipid emulsions were used in the study infants: Group 1 (n = 40) received fish-oil based lipid emulsion (SmofLipid®) and Group 2 (n = 40) soybean oil based lipid emulsion (Intralipid®).
Main outcome measures: The development of retinopathy of prematurity and the need for laser photocoagulation were assessed.
Results: The maternal and perinatal characteristics were similar in both groups. The median (range) duration of parenteral nutrition [14 days (10–28) vs 14 (10–21)] and hospitalization [34 days (20–64) vs 34 (21–53)] did not differ between the groups. Laboratory data including complete blood count, triglyceride level, liver and kidney function tests recorded before and after parenteral nutrition also did not differ between the two groups. In Group 1, two patients (5.0%) and in Group 2, 13 patients (32.5%) were diagnosed with retinopathy of prematurity (OR: 9.1, 95% CI 1.9–43.8, p = 0.004). One patient in each group needed laser photocoagulation, without significant difference. Multivariate analysis showed that only receiving fish-oil emulsion in parenteral nutrition decreased the risk of development of retinopathy of prematurity [OR: 0.76, 95% CI (0.06-0.911), p = 0.04].
Conclusions: Premature infants with very low birth weight receiving an intravenous fat emulsion containing fish oil developed less retinopathy of prematurity.

1. Introduction

Advances in neonatal care have led to increased survival of infants born prematurely. Total parenteral nutrition (TPN) is initiated in very low birth weight (VLBW) infants to achieve the postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postconceptional age. In these infants, full enteral feedings are generally delayed because of the severity of medical problems associated with prematurity, such as feeding intolerance or necrotizing enterocolitis (NEC).

The importance of ω−3 polyunsaturated fatty acids (PUFAs) has been shown in fetal and neonatal development, especially for brain and retinal tissues which are highly dependent on ω-3 PUFAs especially docosahexaenoic acid (DHA) [1]. However, preterm infants are often deficient of ω−3 PUFAs because the most of ω−3 PUFAs are transferred from mother to fetus in the third trimester of pregnancy [2,3]. Moreover, preterm infants have a very limited ability to synthesize DHA from the α-linoleic acid. The major source of DHA after birth for preterm newborns is breast milk or DHA-enriched formula [4]. It is well known that the main sources of lipids for VLBW infants are fat emulsions given as components of TPN within the first two to three weeks of life.

Intravenous lipid emulsions are important components of TPN. They contain essential fatty acids and provide a key source of calories which is critical for growth and development of infants not receiving enteral feedings. Conventional lipid emulsions derived from soybean oil contain a high share of ω−6 PUFAs (mainly linoleic acid). The lack of ω−3 PUFAs might cause major problems on growing infant and can be adjusted by ω−3 PUFAs containing lipid emulsions which are the main sources of lipid in infants born prematurely. A new generation lipid emulsion SMOFlipid contains a mixture of soybean oil, medium chain triglycerides (MCT), olive-oil, fish-oil (ω−3 PUFA) and α-tocopherol [5]. The routine use of SMOFlipid within a TPN regimen is shown to be well tolerated, safe and beneficially modulating the fatty acid profile in preterm infants [6]. In a recent research, Gura et al. showed the safety

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and efficacy of a fish-oil-based fat emulsion on parenteral nutrition-associated liver disease in infants [7].

There are limited data on retinal effects of ω−3 PUFA supplementation on preterm infants [8,9]. Therefore, in this study, we investigated whether VLBW infants who received a fish-oil emulsion administered from the first day of life would exhibit or not lowered risk of ROP compared with infants who received a soybean oil emulsion.

2. Patients and methods

2.1. Design and setting

From 01 January, 2013 to 31 July, 2013, a prospective, blinded, single center, randomized controlled trial was conducted in the neonatal intensive care unit (NICU) of Ankara Dr. Sami Ulus Maternity and Children Research and Training Hospital, a level III neonatal center in Turkey.

2.2. Patients and study protocol

During the study period, preterm infants admitted to NICU were included. Infants who weighed <1500 g and delivered prematurely before the 32nd week of gestation were eligible for the study. Infants with major congenital anomalies, congenital infections and inborn metabolic errors were excluded from the study.

Informed and written parenteral consents were obtained before randomization. Infants who needed TPN were treated with a volume composition of lipid emulsions that were both supplied by Fresenius Kabi AB (Uppsala, Sweden). Study infants were randomly assigned to one of the two groups by balanced blocks using sealed envelopes. Stratification was not included in the block design.

- Group 1: Fish-oil emulsion (20% SMOFlipid: soybean oil 60 g/dL, MCT 60 g/dL, olive oil 50 g/dL, fish oil 30 g/dL, egg phospholipids 12 g/dL, glycerol 25 g/dL, vitamin E 200 mg α-TE/L).
- Group 2: Soybean oil emulsion (20% Intralipid: soybean oil 200 g/dL, egg phospholipids 12 g/dL, glycerol 22,5 g/dL, vitamin E 57 mg α-TE/L).

Group assignment was made by the investigator (last author) who was not involved in the care of the infants. A member of the TPN team who was blinded and not involved in the care of infants followed orders from the sealed envelope prepared by the investigators. Nurses and doctors responsible for the infants were also blinded to the group assignment.

TPN was started with intravenous glucose and amino acid solution (1 g/kg) in the first day of life. In both groups, the lipid emulsions were administered from the first day of life as a continuous infusion for 24 h per day. The initial daily dose for infants with a birth weight of <1000 g was 0.5 g of lipids per kg of body weight. Respectively, the initial dose for infants with birth weight of >1000 g was 1.0 g of lipids per kg of body weight. It was increased by 0.5 to 1.0 g of lipids per kg body weight every 24 h to a maximum of 3.0 g of lipids per kg of body weight/day. Infants also received trace elements, water and lipid soluble vitamins as standard part of TPN protocol.

With regard to enteral feeding, infants in both groups were fed initially and advanced at 20 mL of breast milk (an average content of lipids ranged from 3.8 to 4.3 g per 100 mL) and/or preterm formula (Prematil-LCP®, Milupa, GmbH, Friedrichsdorf, Germany; 3.9 g of lipids per 100 mL) enriched with ω−3 long-chain polyunsaturated fatty acids per kg per day, according to feeding tolerance. Thirty-two infants in Group 1 (80%) and 30 infants in Group 2 (75%) received their own mother's breast milk. The intravenous lipid infusion as a component of TPN was progressively replaced with enteral intake so as to maintain 3.0 g of lipids per kg of body weight/day. The dosages and schedule of lipid administration were similar in both groups.

Demographic and clinical data including the patients' gender, gestational age, birth weight, APGAR score, severity of disease score (SNAPPE-II; The Score for Neonatal Acute Physiology Perinatal Extension), the presence of associated disorders such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) (grade ≥ 2), necrotizing enterocolitis (NEC) (grade ≥ 2), and CLD (oxygen dependency beyond 36 weeks of corrected age) with diuretic or steroid, cholestasis (defined as serum direct bilirubin value of 1.0 mg/dL, if the total bilirubin level was <5.0 mg/dL or direct bilirubin value of >20% total bilirubin if the total bilirubin level was >5.0 mg/dL), ROP and need for laser photocoagulation, metabolic disturbances such as hypoglycemia/hyperglycemia and culture proven sepsis were recorded. The number of red blood cell (RBC) transfusion, duration of mechanical ventilation, duration of oxygen, duration of TPN and length of hospitalization were noted. Laboratory data including whole blood count, creatinine, triglyceride, total/direct bilirubin, alanine amino transferase (ALT) and gamma-glutamyl transpeptidase (GGT). Laboratory values were prospectively measured biweekly.

2.3. Outcomes

Primary outcomes were the development of ROP and the need for laser photocoagulation. Secondary outcomes including cholestasis, nosocomial infections, NEC, intraventricular hemorrhage, and chronic lung disease were analyzed in both groups.

2.4. Ophtalmological assessment

In both groups, the level of oxygen saturation was monitored by pulse oximetry within the first minutes of life and continued until the infant was breathing ambient air and did not require respiratory support. Adjustments in supplemental oxygen to maintain the target level of oxygen saturation between 90 and 95 (ranges identical for both groups) were performed by the clinical nurses.

The initial ROP examinations were performed when corrected age was 31 weeks in infants with gestational age of ≤27 weeks, while the infants born at or beyond 28 weeks were examined by the postnatal fourth to fifth weeks. All fundus examinations were performed by the same pediatric ophthalmologist who was blinded to the group assignment. The follow-up examinations were performed once a fortnight in patients with low-risk pre-threshold disease, and at least once a week for ones with high-risk pre-threshold disease. Infants with normal vascularization of the retina to the periphery were not re-examined. The patients were treated with indirect ophthalmoscopic argon LP [OcuLight GL (532 nm) Laser Photo-coagulator] of the entire avascular retina with near confluent burns when type 1 ROP developed, as determined by the Early Treatment for Retinopathy of Prematurity (ETROP) study [10].

2.5. Ethics

The study protocol was approved by the Local Ethics Committee. All parents were fully informed about the investigational nature of this study as well as its aim. A written consent was obtained from all parents. This trial has been registered at www.clinicaltrials.gov (identifier NCT01875510).

2.6. Sample size calculation and statistics

According to our previous research the incidence of ROP among VLBW infants was ~30%. We hypothesized that fish-oil lipid emulsion in VLBW might decrease the rate of ROP. A power analysis showed that setting the error 0.05 with 72.9% power and an absolute reduction of the incidence of ROP by 20%, the total number needed to verify our hypothesis was 80 (40 in each group).

SPSS 17.0 (SPSS, Chicago, IL) was used for statistical analysis. The Kolmogorov–Smirnov test was used to determine the shapes of the distribution of variables. Data are expressed as the arithmetic