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Original Article

Using Parenteral Fish Oil From Birth May Improve Short and Long Term Outcome in Preterm Infants

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ABSTRACT

Background: Lipids are a crucial component of parenteral nutrition in its entirety. This study aimed to compare the short—and long-term outcomes of lipid solutions containing fish oil and standard parenteral lipid solutions in total parenteral nutrition of premature neonates.

Methods: Preterm infants weighing less than 1500 grams or 32 weeks gestation admitted to Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital Neonatal Intensive Care Unit between January 2018 and January 2020 were included in this retrospective cross-sectional study. Infants receiving only 3 g/kg/day Clinoleic were enrolled in Group 2; infants receiving 1 g/kg/day Omegaven plus 2 g/kg/day Clinoleic were enrolled in Group 1. Weight at discharge, laboratory data (liver enzymes, bilirubin levels), and long-term results were compared.

Results: The study comprised 70 newborns, and 35 of them were in Group 1. Group 1 had a considerably lower direct bilirubin level (d bil p value^{u}; 1st week $_{p=0.03}$, 2nd week $_{p=0.87}$, 3rd week $_{p=0.02}$). The omegaven group had a considerably higher weight upon discharge (p=0.02). Long-term neurodevelopmental results did not differ across the groups (MDI score $_{p=0.33}$, PDI score $_{p=0.11}$, NDI positivity $_{p=1.00}$, MDP $_{p=0.81}$).

Conclusion: We demonstrated that the weight at discharge and laboratory measurements improved with Omegaven support. Early exposure to very high levels of oxidative stress may cause infants to employ their antioxidant system as a parenteral support system.

Keywords: Fish oil, Preterm infant, Outcomes, Total parenteral nutrition

Introduction

Despite the technological advances in perinatology, prematurity is still the most common problem in developing countries. Preterm infants generally cannot tolerate enteral feeding due to intestinal immaturity, and parenteral nutrition is essential in these babies. Parenteral nutrition (PN) is used to supply infants with daily protein, lipids, and other requirements (1). There is no doubt that an important component of parenteral nutrition is lipid emulsions (LE), and many LEs have been developed over the years. Pure soybean oil and olive oil-based lipid emulsions have been the standard solutions for the last few years (2, 3). Despite there being no ideal solution, olive oil-soybean oil (OO/SO) based LEs had higher alfa-tocopherol, omega-6, and omega-9 polyun-saturated fatty acids (PUFA) (4,5). It is generally well tolerated in preterm babies and positively affects the cardiovascular system, growth, development, and inflammatory processes (6, 7). However, there is no omega-3 in these LEs. The new model of LEs, which contains olive oil, soybean oil, fish oil, and medium chain triglycerides (MC), has good results in a few studies, but it is not available in every neonatal

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intensive care unit (NICU) (8). Fish oil (FO) based LEs are good enough to provide docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (9, 10). Both DHA and EPA affect inflammatory pathways by decreasing the proinflammatory cytokines and increasing the anti-inflammatory cytokines (9). According to current research, intravenous fish oil increases bile acid mechanisms, decreases cholestasis, and enhances biliary flow (11).

This study evaluated the short—and long-term effects of two distinct lipid LEs on preterm newborns.

Methods

This retrospective cross-sectional trial was conducted at xxx Hospital. Xxx Hospital has 58 incubators with 20 level IV beds in the NICU and nearly 1500 infants admitted to NICU during the one year. Preterm babies with gestational age ≤ 32 weeks and /or birth weight ≤ 1500 g were included in the trial between 1 January 2018 and 1 January 2020.

Study Design

Infants given 100% FO emulsion (*Omegaven, Fresenius Kabi*) together with Clinoleic in group 1 (1:2 ratio), infants given OO/SO LE (Clinoleic, Baxter, Lessines, Belgium) as 'OO/SO lipid' in group 2, was recorded retrospectively.

Exclusions from the study were infants with prenatal asphyxia, congenital cardiac disease, metabolic abnormalities, congenital severe defects, and infants with LEs lasting shorter than seven days. Parents' signed and informed consent was obtained.

Procedure

All infants were started LEs in the first 24-48 hours at 1g /kg body weight per day and increased daily. Within a week, the dosage of omegaven was raised from 0.2 g/kg per day to a maximum of 1 g/kg per day. ClinOleic accounted for the remaining 2 g/kg/d. In accordance with Turkish Neonatal Society guidelines on parenteral feeding in preterm newborns, amino acids were administered at a rate of 3–4 g/kg/d and glucose at a rate of 6–10 g/kg/d. Additionally, all parenteral nutrition was supplemented with electrolytes, trace elements, and vitamins (12). The hospital pharmacy's central or peripheral intravenous preparation unit compounded the PN in accordance with the manufacturer's instructions. In accordance with our unit protocol, which is based on guidelines from the Turkish Neonatal Society, all PN prescriptions were written by neonatologists and/or neonatology fellows and were specifically tailored to the needs of each patient. These factors included clinical condition, gestational week, age, weight, and laboratory results (12). The peripheral or central venous line was used to deliver both bags of the prepared PN, which contained vitamins and lipids in one bag and all additional supplements in another. The vitamin supply was a 1:1 mixture of Soluvit (Fresenius Kabi) and Vitalipid Infant (Fresenius Kabi). The earliest feasible commencement of enteral feeding was made. The team, which included a pediatric surgeon, neonatologist, fellows in neonatology, and NICU nurse, monitored the infants daily.

Data Collection

Serum electrolytes, complete blood counts, liver enzymes, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, gamma glutamate transferase (GGT), serum albumin, and C-reactive protein (CRP) were among the blood parameters that were examined once a week. Weight gain was noted daily and weekly. Morbidities during hospitalization (PDA (patent ductus arteriosus), IVH (intraventricular hemorrhage), BPD (bronchopulmonary dysplasia), stage ≥ ROP (retinopathy of prematurity), stage ≥ 2 NEC (necrotizing enterocolitis), culture positive sepsis), mortality and duration of hospitalization stay were compared between groups.

The medical record system provided all of these data and the short-term results. The study did not include patients whose data were lacking or inconsistent with this follow-up process.

Neurological Developmental Assessment

The premature and risky baby outpatient clinic carried out post-discharge follow-up of these infants with the support of developmental and behavioral pediatric specialists and child neurology, and their physical and mental development was closely monitored according to their corrected ages.

The Bayley scale was once again cited as the most widely used method of evaluating neuromotor and developmental outcomes in a systematic evaluation of the effects of early treatments on motor development (13).

When the infants were between 18 and 24 months old, the same two developmental and behavioral pediatric specialists contacted the families through their outpatient control to

administer the "Bayley Scales of Infant Developmental Assessment Scale II" (BSID) with their consent. The evaluation scales used for Bayley and Bayley-II were the mental development index (MDI) and the psychomotor development index (PDI). While the PDI assesses gross and fine motor development, the mental development index looks at language and cognitive development (14).

Cerebral palsy, bilateral hearing loss or blindness, or an MDI or PDI score below 70 were considered indicators of neurodevelopmental retardation. However, a score between 70 and 84 was considered minimally delayed performance (MDP) (15). As far as we know, the Bayley-III scale requires further testing, our outpatient clinics are busy, and appointment times are short. Thus, Bayley-II was selected for this study's neurodevelopmental assessment.

Statistical Analysis

The PAST 3 (Hammer,Ø., Harper, D.A.T., Ryan, P.D. 2001) and SPSS 25.0 (IBM Corporation, Armonk, New York, United States). Programs for paleontological statistics were utilized to analyze the variables. The Shapiro-Wilk and Levene tests were used to assess the conformance of univariate data to the normal distribution. In contrast, the Mardia (Dornik and Hansen Omnibus) test and the Box's M test were used to assess the conformity of multivariate data to the normal distribution. The chi-square test and Fisher's exact test were used to compare the relationships of categorical variables with each other. The Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups according to quantitative data. In comparing the quantitative variables of dependent quantitative measurements, Friedman's Two-Way test was used together with the Monte Carlo Simulation technique results.

In contrast, Dunn's Test was used for the Post Hoc analysis. The quantitative variables were expressed as Mean ± SD [Standard Deviation] and Median [Minimum / Maximum], while categorical variables were shown as n [%] in the tables. The variables were analyzed at a 95% confidence level and were considered significant when p value was less than 0.05.

The post hoc analysis had a total sample size of 70 with a 2-sided error of 8%, and the power of the study was 80%.

Ethical approval

Since hospital data were used in this retrospective study, local permission approval was obtained on 23. 2.2021 (Number: E-13399118-799) from the xxx hospital. The study was approved by the Clinical Research Ethics Committee of xxx University (2024/04; 24-109), and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Demographic Characteristics

A total of 70 infants, 35 of whom were in each group, were included in the study. The demographic characteristics of all included infants are given in Table 1. There was no difference in terms of gender, gestational week, birth weight, breastfeeding rates, duration of lipid administration, transition to total enteral feeding (male gender $_{p=0.3}$, gestational week $_{p=0.5}$, birth weight $_{p=0.9}$, breastmilk $_{p=0.5}$, duration of lipid administration $_{p=0.1}$, T/E duration $_{p=0.6}$, respectively).

Short-term Outcomes

It was found that AST, ALT, and total bilirubin values in Group 1 varied according to weeks ($AST_{p=0.001}$, ALT $_{p<0.001}$, t bil $_{p<0.001}$, respectively). Direct bilirubin values in Group 1 were statistically lower in the first and third weeks

Table 1. Characteristics of infants

	Group 1 (Omegaven + Clinoleic) (n:35)	Group 2 Clinoleic (n:35)	P
Gestational age (wk)*	29.6 ± 2.4	30 ± 2.1	0.5
Birth weight (gram)*	1300 ± 346	1295.5 ± 269	0.9
Male gender (%)	14 (40)	19 (54)	0.3
Breastmilk (%)	18 (51)	22 (62)	0.5
Duration of TPN (day)*	9.0 ± 4.8	11.2 ± 8.2	0.1
T/E duration (day)*	16.3 ± 9.1	17.3 ± 11.4	0.6
Time to reach birth weight (day)*	9.0 ± 4.8	11.2 ± 8.2	0.1

*as presented mean ±SD

Table 2. Laboratory evaluation of the infants

	Measurements			Pairwise Comparisons				Changes by Weeks		
	1st Week	2nd Week	3rd Week		Between Measurements			(2-1)	(3-1)	(3-2)
	Median (Min/ Max)	Median (Min/ Max)	Median (Min/ Max)	P Value[f]	(2-1)	(3-1)	(3-2)	Median (Min/ Max)	Median (Min/ Max)	Median (Min/ Max)
AST										
omegaven	33(17/68)	26(17/68)	25(15/260)	0.001	0.004	0.002	0.999	-7(-48/13)	-5(-36/211)	-3(-15/220)
clinoleic	33(18/180)	29(18/180)	28(15/67)	0.089	ns.	ns.	ns.	-2(-34/22)	-4(-158/18)	-4(-158/24)
P value[u]	0.495	0.056	0.401					0.013	0.314	0.186
ALT										
omegaven	6(60/23)	7(50/17)	9(60/80)	<0.001	0.999	0.001	0.018	0(-120/7)	2(-90/72)	2(-70/65)
clinoleic	7(50/35)	8(50/35)	10(60/26)	0.001	0.454	0.002	0.146	1(-30/6)	2(-280/17)	2(-280/18)
P value[u]	0.305	0.259	0.497					0.362	0.773	0.912
TBIL										
omegaven	6.7(3.70/17.6)	6.4(0.50/11.3)	5.1(0.50/77)	<0.001	0.999	0.004	0.002	-1(-10.50/3.8)	-2(-10.50/70.3)	-1.2(-5.70/69.3)
clinoleic	8.2(1.20/15)	6(0.50/12)	4.6(0.40/9.3)	<0.001	0.021	<0.001	0.007	-0.7(-5.70/4.7)	-3.1(-7.50/2.2)	-1.1(-4.40/0.8)
P value[u]	0.813	0.780	0.365					0.710	0.449	0.465
DBIL1										
omegaven	0.4(0.30/0.7)	0.5(0.23/1.1)	0.4(0.20/4)	0.296	ns.	ns.	ns.	0.1(-0.15/0.4)	0(-0.34/3.6)	0(-0.78/3.6)
clinoleic	0.5(0.31/1.7)	0.5(0.10/1.4)	0.5(0.16/2.1)	0.767	ns.	ns.	ns.	0(-0.34/0.6)	0(-0.44/1.2)	0(-0.37/0.8)
P value[u]	0.034	0.872	0.029					0.119	0.636	0.117
PLT1										
omegaven	234(72/466)	285(30/629)	350(90/1890)	0.062	ns.	ns.	ns.	25(-149/228)	48(-138/1582)	28(-196/1538)
clinoleic	226(112/324)	270(89/480)	327(100/577)	<0.001	0.008	0.001	0.999	46(-162/205)	75(-172/284)	7(-158/255)
P value[u]	0.352	0.663	0.556					0.706	0.806	0.928
Alb1										
omegaven	3(2.1/3.8)	3(2.3/3.6)	3(2.3/3.7)	0.736	ns.	ns.	ns.	0(-0.8/0.6)	0(-0.7/0.7)	0(-0.4/0.7)
clinoleic	3(2.2/3.7)	3.1(2.3/3.8)	3(2.6/3.5)	0.039	0.999	0.320	0.020	0(-0.7/0.7)	-0.2(-0.7/0.7)	-0.1(-0.6/0.5)
P value[u]	0.240	0.074	0.836					0.611	0.243	0.021
GGT1s										
omegaven	104(380/576)	90(420/371)	96(240/800)	0.405	ns.	ns.	ns.	-4(-2050/256)	-2(-1440/696)	-1(-1600/721)
clinoleic	82(190/286)	115(350/350)	130(310/446)	0.084	ns.	ns.	ns.	14(-1220/159)	13(-1190/357)	-1(-750/260)
P value[u]	0.028	0.443	0.445					0.007	0.216	0.771

[f]Friedman test (Monte Carlo); Post Hoc Test: Dunn's Test. [u]Mann Whitney U test (Monte Carlo), Min.: Minimum, Max.: Maximum, ns.: Not Significant

compared to Group 2 (d bil p value[u]; 1st week $_{p=0.03}$, 2nd week $_{p=0.87}$, 3rd week $_{p=0.02}$). The analysis of all laboratory parameters according to the weeks is given in Table 2.

Although the surfactant requirement was statistically significantly higher in Group 1, there was no difference between groups in terms of PDA, IVH, BPD, stage ≥ 2 ROP, stage ≥ 2 NEC, culture-positive sepsis, duration of hospital stay, and mortality (Figure 1 & Table 3). The weight discharge was statistically significantly higher in Group 1 compared to Group 2 (p=0.02).

Neurodevelopmental Outcomes

In the neurodevelopmental evaluation of the infants' 18-24 months follow-up, BAYLEY II scores did not show any difference between the MDI and PDI scores. Blindness was not seen in any infants during the follow-up (MDI score $_{p=0.33}$, PDI score $_{p=0.11}$, NDI positivity $_{p=1.00}$, MDP $_{p=0.81}$, respectively) (Table 4).

Table 3. Comparison of short-term outcomes in infants

	Group 1 (Omegaven + Clinoleic) (n:35)	**Group 2 Clinoleic (n:35)**	**p**
Surfactant dosage*	0.8 ± 0.6	0.4 ± 0.49	***0.002***
hsPDA (n, %)	8 (22)	6 (17)	0.76
Mild IVH (n, %)	4 (11)	6 (17)	0.73
Stage ≥2 NEC (n, %)	1 (2)	0 (0)	1.00
Stage ≥2 ROP (n, %)	5 (14)	5 (14)	1.00
BPD (n, %)	1 (2)	2 (4)	1.00
Total O_2 exposure (day)*	11.6 ± 13.4	11.2 ± 18.0	0.87
Duration of hospitalization (day)*	48.4 ± 21.4	41.4 ± 19.6	0.31
Weight at discharge (gram)*	2026 ± 186.4	1938.7 ± 128.4	***0.02***
Mortality (n, %)	0	0	*NS*

*as presented mean±SD
hsPDA: hemodynamically significant patent ductus arteriosus,
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
ROP: rethinopathy of prematurity
BPD: bronchopulmonary displasia

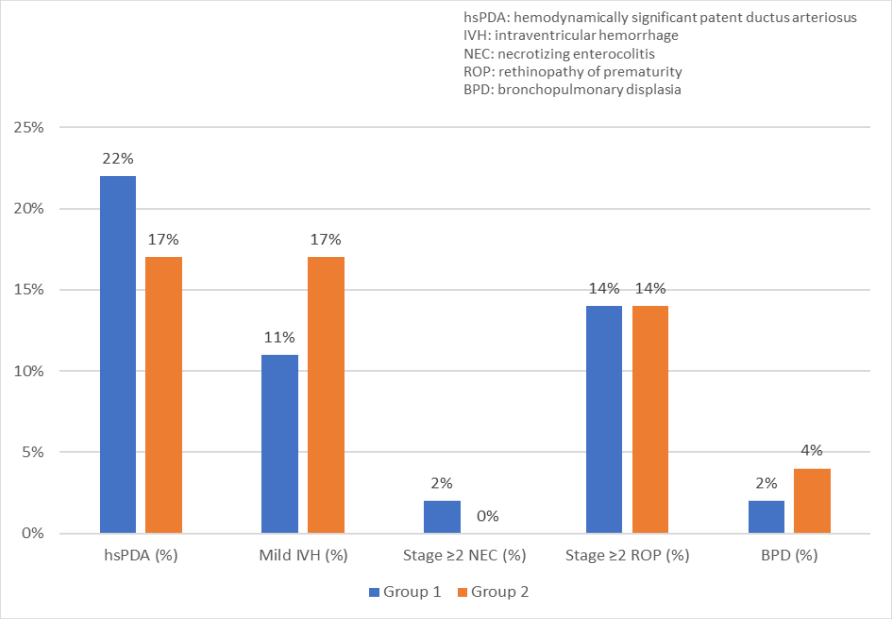

Figure 1. Short-term outcomes of study groups

Table 4. Neurodevelopmental evaluation of groups

	Group 1 (Omegaven + Clinoleic) (n:35)	Group 2 Clinoleic (n:35)	p
MDI score*	103.3 ± 9.4	100.5 ± 10.7	0.33
PDI score*	103.6 ± 10.3	98.6 ± 10.6	0.11
NDI* Positivity (n, %)	2 (4)	1 (2)	1.00
MDP (n, %)	5 (14)	7 (20)	0.81
Blindness (n, %)	0	0	NS
Deafness (n, %)	0	0	NS
CP (n, %)	0	0	NS

*as presented mean ±SD
MDI- Mental developmental index, PDI- Psychomotor developmental index,
NDI*- Neurodevelopmental retardation index defined as the presence of one or more of the following: 1) Moderate to severe cerebral palsy with functional losses, 2) Bilateral hearing loss and blindness, 3) Bayley-II MDI or PDI score <70
MDP- Mildly delayed performance, defined as the presence of Bayley-II MDI or PDI score 70-84
CP - Cerebral palsy

Discussion

In this study, supplementing the fish oil was compared with the standard lipid solutions since the beginning of parenteral nutrition, and its short and long-term effects were evaluated. The supply of fish oil provided improvement in laboratory parameters in the short term, and the weight discharge was higher in infants given fish oil. However, long-term outcomes were similar between groups aged 18-24 months. There was no difference between the BAYLEY II results.

Lipids are TPN's most important energy and essential and long-chain fatty acid sources. Soy and olive oil-based lipid solutions have been used for parenteral nutrition for many years. However, due to the phytosterols they contain, lipids are thought to have a negative effect on biliary secretion and play a role in the development of cholestasis (16). Unlike other solutions, lipid solutions containing fish oil do not contain phytosterols (17). On the other hand, fish oil-containing solutions are rich in n-3 fatty acids and have been shown to reduce hepatic inflammation (18). Compared to soy-based lipid solutions, clinical studies show that fish oil-containing lipid solutions reduce cholestasis findings in preterm infants (16, 19). The high amount of phytosterol was seen in the soybean-based LEs in cholestasis, and phytosterol collection is caused by a decrease in bile flow in an experimental model and infants (20, 21). In a study by Puder et al. (22), 42 babies with cholestasis, whose average gestational age was 30 weeks and average postnatal age was 12 weeks, were given lipid support only with Omegaven and it was found that their cholestasis levels decreased within approximately 12 weeks.

Angsten et al. (23) provided fish oil supplements to 14 cholestasis cases in addition to the standard lipid solution containing olive and soy oil. They showed that the level of cholestasis decreased within 2.9 months. The present study differs from all other studies in the literature since a standard lipid solution has been given with a fish oil supplement since the beginning of parenteral nutrition support. Although cholestasis was not observed in any of the babies, it is remarkable that the laboratory values were lower in the group in which fish oil was added.

Preterm babies are more sensitive to oxidative stress due to their low antioxidant capacities (24). This suggests that high alpha-tocopherol levels contained by fish oil solutions will be more suitable for preterm babies (24). Although olive oil-containing solutions have long-chain fatty acids, the rates are rather low compared to solutions containing fish oil, and the solutions containing fish oil differ as they are the only solutions containing eicosapentaenoic acid. Previous studies stated that the frequency of retinopathy may decrease in light of these mechanisms (25-27). In the present study, there was no difference between the two groups regarding the frequency of ROP. Although surfactant and intubation requirements are higher in the group containing fish oil, the similar rates of bronchopulmonary dysplasia in the cases show that the solutions containing fish oil may be associated with higher antioxidant content. Antioxidants used in preterm babies exposed to very intense oxidant stress in the early period may be promising as a supportive parenteral product (24). However, studies involving a large number of cases are needed to make clear comments on this issue. Very few studies on this subject exist in the literature (26). In the Deshpande et al. (28) study, preterm babies at 23-30 gestational weeks were given OO/SO LEs and FO LEs, and no significant difference was found between laboratory values and short-term results.

Similarly, Najm et al. (29) and Unal et al. (24) compared SMOF lipid and Clinoleic LEs and showed no difference in short-term outcomes. In a recent study, Yildizdas et al. (30) investigated the effects of OO/SO and FMOS LEs on cholestasis, levels of antioxidant enzymes, and lipid peroxidation. They found that oxygen radical levels were higher in the OO/SO group, and cholestasis was significantly lower in the FMOS group but showed similar short-term outcomes.

Lipid solutions with fish oil content have been used in the literature, usually in infants with cholestasis. However, these babies with limited antioxidant capacities are intensely exposed to oxidant stress since the first day, especially in the early period. Therefore, this made us think that using a supportive lipid solution in the early period created a suitable mixture during the parenteral feeding period.

SMOF, a lipid solution containing a mixture of omega-6 and omega-3, has been increasingly used to prevent this deficiency, especially in babies with low birth weight and who cannot be fed enterally. Although small-scale studies have shown that it reduces the frequency of ROP compared to mixtures containing only soybeans, no clear advantage has been reported in the Cochrane meta-analysis (31). However, in the the results of the present study, mixtures that will be formed with fish oil in the ratio of 2/1 in units where SMOF cannot be given or is not available seem suitable.

Even with its advantages, our study has many shortcomings. The first disadvantage was that the results were restricted to a single-center scenario. The second limitation was the small number of patients and the study's retrospective design.

Based on our study, designing a multicenter, prospective randomized controlled study on this subject, for which the literature does not provide enough information and experience, will shed light on the future.

Conclusion

Finally, we conclude that adding fish oil to parenteral nutritional solutions from the beginning of life will provide favorable results in longer case-control series.

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Conflicts of interest

The authors declare no conflict of interest.

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