Progress in Nutrition 2022; Vol. 24, N. 3: e2022078 DOI: 10.23751/pn.v24i3.12444

Original article

Effect of Omega-3 Fatty Acid Added to Parenteral Nutrition on Inflammatory in Preterm Infants

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Abstract. *Objective:* This study aimed to investigate the effect of omega-3 fatty acid addition to Total Parenteral Nutrition (TPN) on the inflammatory process and clinical outcomes. *Methods:* The study included 51 infants who were in the Neonatal Intensive Care Unit (NICU) and fed by TPN for minimum 10 days, with a gestational age of ≤32 weeks and a birth weight of ≤2500 g. The preterm infants fed by TPN with 80% omega-9 and 20% omega-6 fatty acids were determined as Group 1(n:26) and by TPN with added omega-3 fatty acid (1.0g/day) as Group 2 (n:25). This retrospective study retrieved demographic characteristics, anthropometric measurements, nutrition therapy details, comorbidity development, inflammatory markers, and laboratory and clinical results from patient files. Those who received exchange transfusions and who received TPN for less than 10 days were excluded from the study. *Results:* Comorbidity developed in 35% of Group 1 and 28% of Group 2, with no difference between the groups ($p < 0.05$). There was no difference in gestational week at birth, birth weight, duration of mechanical ventilation (MV), duration of oxygen support, and maternal age between the two groups ($p < 0.05$). There was no difference in the carbohydrate (CH), protein and lipid levels, and glucose infusion rate (GIH) between the two groups ($p < 0.05$). In Group 2, the daily amount of omega-3 fatty acid was increased by 1.0±0.1 g/day, accounting for 7.7±0.03% of the total energy. There was a significant decrease in the blood levels of Aspartate Aminotransferase (AST) and Total Bilirubin (T.Bil) on day 10 in Group 2 ($p < 0.05$). Procalcitonin (PCT) significantly decreased on days 1, 4, 7, and 10 in both groups ($p < 0.05$). The difference in C-Reactive Protein (CRP) on days 4 and 10, and PCT and Neutrophil-to-Lymphocyte Ratio (NLR) on days 1, 4, 7, 10 was insignificant, with lower values in Group 2. *Conclusion:* The present study established a low level of positive changes in inflammatory findings and a decrease in liver function test results with the addition of fish oil to TPN. The different fatty acid contents of ILEs, the optimum ratio between the fatty acids, and the amount and duration of use affect the clinical outcomes. Further studies are needed to determine a safe, adequate dose and appropriate fatty acid profile.

Key words: Omega-3 fatty acid, inflammation markers, premature, parenteral nutrition

Introduction

Complications such as immature gastrointestinal (GI) tract and respiratory muscles, surfactant deficiency, hypothermia, hypoglycemia, sepsis, and necrotizing enterocolitis (NEC) are common in preterm infants followed in the Neonatal Intensive Care Unit (NICU). In particular, immature GI tract and digestive enzyme deficiency, and the incomplete development of sucking-swallowing function prevent

adequate enteral nutrition. According to recent recommendations, it is safe to initiate parenteral nutrition (PN) in the first days after birth, if possible, within the first hours of life, and should be maintained until adequate enteral nutrition is achieved. Especially a high-protein and an essential fatty acid-diet was shown to result in successful growth, neurological development, and an increased lean muscle mass in the first two years of life in preterm infants [1-4].

Linoleic acid (omega-6, LA) and **α**-linolenic acid (omega-3, ALA) are essential fatty acids. LA is metabolized to arachidonic acid (AA) and ALA to its subderivatives; docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). AA and DHA are known to accelerate growth and neural development. DHA is the primary structural lipid component of the central nervous system, constituting 30–50% of the neuronal plasma membranes [5]. Studies support that the use of high-dose DHA or omega-3 fatty acid in preterm infants may play an important role in reducing the risk of bronchopulmonary dysplasia (BPD), NEC, retinopathy of prematurity (ROP), and sepsis [6].

Intravenous lipid emulsions (ILEs) have different fatty acid contents. Different compositions of ILE are related to oxidation, inflammation, and disease. ILEs also contain phytosterol. Soybean oil-based ILEs contain more phytosterols than olive oil-based ILEs. Therefore, it may contribute to bile flow reduction and intestinal failure-associated liver diseases. In addition, it triggers the development of insulin resistance and an increase in the risk of hyperglycemia in preterm infants. AA forms the 2-series of thromboxanes (TX) and the 4-series of leukotrienes (LT), contributing to the inflammatory process and suppression of cell-mediated immunity. Omega-3 fatty acid and its derivatives EPA/DHA produce the TX3 series and LT5 series, which have anti-inflammatory effects. It has been shown that lipid mediators such as resolvins, protectins, maresins, and lipoxins, the subgroups of omega-3 fatty acid, which have been discovered recently and are also effective in the inflammatory process, limit neutrophil infiltration and increase the macrophage response, playing an important role in the diseases characterized by uncontrolled excessive inflammation [7-9].

Procalcitonin (PCT) is effective in the diagnosis of neonatal sepsis. It may fluctuate in the first hours (< 72 hours) of life. The half-life of C-Reactive Protein (CRP) is 4 to 6 hours, and sepsis can be diagnosed by serial measurements. The use of CRP alone is not recommended because it can also increase in non-infectious inflammatory settings. Neutrophil-to-lymphocyte ratio (NLR) has recently been used as an indicator of subclinical inflammation. Stress-induced immune response is characterized by an increased neutrophil count and a decreased lymphocyte count. Estimated reference range varies across age groups, by sex, and in specific conditions [10-12].

Studies on the use and amount of omega-3 fatty acid in preterm infants and its effect on clinical outcomes are limited. The present study, considering the anti-inflammatory properties of omega-3 fatty acid, aimed to find out the effects of the use and amount of omega-3 fatty acid on the inflammatory process and clinical outcomes, and to understand the safe and effective dose.

Materials and methods

This retrospective study was conducted between 01.01.2019 and 30.02.2021 in neonates staying in NICU, with a gestational age of ≤ 32 weeks and a birth weight of ≤ 2500 g. Infants who received Total Parenteral Nutrition (TPN) for less than 10 days and who received exchange transfusion were excluded from the study. Ethics committee approval OMU Faculty of Medicine Clinical Research Committee (Ethics Committee no: 20.08/46-147, on 03.16.2020). According to the TPN protocol used, amino acid emulsion (1.5 g/kg), lipid emulsion (1 g/kg), and glucose emulsion (4–6 mg/kg/min) were initiated on the first day. Amino acid and lipid emulsions were increased by 1 g/kg every day, increasing the amino acid dose to 4 g/kg and the lipid dose to 3 g/kg. The amount of glucose was adjusted according to the hypo/hyperglycemia status. The target blood sugar level was 60–150 mg/dL. An ILE with 80% olive oil and 20% soybean oil was used in Group 1 (n:26). In Group 2, 1g/kg/day lipid was started and increased up to 3g/kg. 10% omega-3 lipid solution was added to Group 2. 0.7 g of the total lipid requirement was obtained from omega-3 lipid solution. The other part was given from the lipid emulsion of 80% olive oil + 20% soybean oil (Clinoleic). Fish

Oil-based lipids (Omegaven), rich in n-3 PUFA, present a 1:8 ratio of n-6:n-3, and contain high amounts of n-3 family fatty acids (EPA and DHA) and vitamin E. The content of fish oil-based ILE; 100% omega-3 fatty acids; 13-26% EPA and 14-27% DHA. Group 2 (n:25) included infants who received ILE with 10% omega-3 (0.7 g/day) according to the total lipid requirement determined (patients of the physicians preferring to use 10% omega-3 ILE and other oil in combination). In both groups, trace elements (0.25–0.5 mL/kg) and fat/water soluble vitamins (1–2 mL/kg) were added when the TPN treatment was administered for more than three days. According to the tolerance status, enteral feeding was initiated with breast milk, starting from 0.5 mL eight times a day and increasing up to 5mL. The height of the infants was measured in the lying position, the head circumference was measured using a single type of tape measure in the clinic, and the body weight using a Beko BKK-200 baby scale (calibrated every 3 months). Nutrition therapies, anthropometric measurements, and clinical and biochemical test results of infants were retrieved from file records. Statistical analysis was performed using software (SPSS 21.0). From the file records, the blood levels of Aspartate amino transferase (AST), alanine amino transferase (ALT), T. Bil, direct bilirubin (D. Bil), triglycerides (TG), total cholesterol (T. Chol) on days 1 and 10 were recorded. The levels of CRP, PCT, and NLR on days 1, 4, 7, and 10 for both groups were obtained from the files. Statistical Package for Social Sciences 21.0 (SPSS) was used to assess the data. Statistical assessment included repeated-measured analysis, Mann-Whitney U test, Wilcoxon t-test, and Spearman's correlation coefficient. A p value of < 0.05 and < 0.01 was considered statistically significant.

Results

Comorbidities developed in 35% of Group 1 and 28% of Group 2, with no difference between the groups ($p > 0.05$) (Table 1). The comorbidities included respiratory distress, abnormal glycemia, NEC, cholestasis, BPD and infection. Eleven (42%) mothers in Group 1 and 13 (52%) mothers in Group 2 had maternal problems, which included preeclampsia, hypertension, hypothyroidism, gestational diabetes, and infectious diseases. Sepsis developed in 4 (15%) infants in both groups; 1 (3.8%) in Group 1 and 2 (8%) infants in Group 2 died. Group 1 and Group 2 did not differ in maternal problems, sepsis, mortality, gestational age, birth weight, duration of mechanical ventilation (MV), duration of oxygen support, comorbidity rate, and maternal age ($p > 0.05$) (Table 1).

Table 1 shows anthropometric measurements and nutrition therapy details of the groups on day 10. The body weight was 1442.3±477 g, height was 39.5±3.9 cm, and head circumference was 28.4±2.9 cm in Group 1, compared with 1474.8±482 g, 38.9±5 cm, and 29.2±4.3 cm, respectively in Group 2. There was no significant difference in weight, height and head circumference measurements between the two groups ($p > 0.05$). Regarding nutrition therapy details, energy (kcal/day) was 75.8±31.5 kcal, protein content (g/day) was 3.8±1.3 g/day, fat content was 2.6±1.2 g/day, fat % of energy was 34.5±11.7, carbohydrate (CHO) content (g) was 14.9±7.1 g/day, CHO % was 65.5±11.8, and glucose infusion rate (GIR) was 7.1±2.4 in Group 1, while energy was 79.7±30.7 kcal/day, protein content was 3.8±1.2 g/day, fat content (g) was 2.6±1.9, fat % was 32.0±8.5%, CHO content (g) was % 16.2±7.6 g/day, CHO % was 68.0±8.5%, and GIR was 7.6±2.2 in Group 2. There was no significant difference between the groups ($p > 0.05$). In Group 2, the daily omega-3 fatty acid intake was 0.7±0.1 g/day.

There was no difference in CRP, PCT, and NLR between groups 1 and 2 ($p > 0.05$). PCT decreased significantly on day 10 in both groups ($p < 0.05$), while CRP increased insignificantly in Group 1 and decreased insignificantly in Group 2. The decrease in NLR was insignificant in both groups ($p > 0.05$) (Table 3).

Figure 1 shows the graphical variation of the blood CRP, PCT and NLR levels on days 1, 4, 7, and 10 in both groups.

The CRP levels on days 4 and 10, and the PCT and NLR levels on days 1, 4, 7, and 10 were lower in Group 2 than in Group 1.

Discussion

It has been reported that AA, EPA, and DHA have protective effects, leading to regression of lung

Table 1. Characteristics and nutritional information of infants

	Group1 (n:26)		Group 2 (n:25)		
Characteristic	Number	%	Number	%	p
Sex, female	15	58	11	44	0.328
Maternal Problems	11	42	13	52	0.488
Sepsis	4	15	4	16	1.000
Mortality	1	4	2	8	0.610
Comorbidity	9	35	7	28	0.480
	Mean±SD		Mean±SD		
Gestational age	29.6±2.7		29.2±2.1		0.318
Birth weight (g)	1317.1±384.3		1272.0±440.3		0.701
Duration of MV (day)	5.6±8.1		10.9±19.5		0.478
Oxygen support (day)	10.8±8.7		12.1±10.9		0.925
Maternal age (y)	30.7±5.5		29.4±5.2		0.382
Weight (g)	1442.3±477.3		1474.8±482.3		0.810
Length (cm)	39.5±4.0		38.9±5.1		0.642
Head circumference (cm)	28.4±3.0		29.2±4.4		0.910
Calorie (kcal)/day	75.8±31.5		79.7±30.7		0.814
Protein (g)	3.8±1.3		3.7±1.2		0.728
Lipid (g)	2.6±1.2		2.6±1.0		0.944
Lipid % of T. calorie	34.5±11.8		32.0±8.5		0.389
Carbohydrate (g)	14.9±7.1		16.2±7.6		0.270
Carbohydrate % of T. calorie	65.5±11.8		68±8.5		0.389
GIR	7.1±2.4		7.6±2.2		0.447
Omega-3 fatty acid (g)	0.0		1.0±0.1		
% omega-3 fatty acid of T. calorie	0.0		7.7±0.03		

MV: Mechanical ventilation, GIR: glucose infusion rate, T. calorie: total calorie, SD: standard deviation.

The ALT and T. Bil levels on day 10 were significantly different in both groups ($p < 0.05$). On day 10, Group 1 had a significant decrease in AST and increase in T. Chol ($p < 0.01$), while AST and T. Bil decreased, and T. Chol increased significantly in Group 2 ($p < 0.05$) (Table 2).

injury in preterm infants [13]. In the present study, a difference in MV and oxygen support would be expected in Group 2. We believe that such difference is due to a small amount of AA fatty acid included the PN received by both groups or the low amount of added EPA and DHA. An average of 0.7 g/day omega-3 fatty acids (133 mg EPA + 140 mg DHA) was added in Group 2 (Table 1), which fell behind the recommended dose based on an average of 1474 g body weight.

Overall, the results of blood liver function tests were lower in Group 2 after the study, but there was no significant difference (Table 2). T. Bil was significantly decreased in Group 2. Previous studies established similar liver functions, protein and albumin levels in the groups received soybean oil-based, fish oil-added TPN, and olive oil-based TPN, and found that different lipid solutions did not affect liver function tests, and cholesterol and TG levels were similar [14-16]. The present study found consistent results in terms of liver function tests.

The amount of phytosterols, which pose a risk for cholestasis, is 383 mg/L in soy-based ILE, lower in olive oil-based ILE (237mg/L), and negligible in fish oil. The use of olive oil-based ILE in Group 1 may have a protective effect on liver functions. Olive oil has

Table 2. Biochemical test results of the groups

		Group 1 (n:26)	**Group 2 (n:25)**	
	Days	Mean±SD	Mean±SD	p
AST (U/L)	1.	58.6±36.1	51.4±49.1	0.097
	10.	27.9±13.5	30.8±17.4	0.050
p		<0.01	<0.05	
ALT (U/L)	1.	7.2±3.7	25.6±73.2	0.115
	10.	8.6±4.0	16.7±15.7	<0.05
p		0.108	0.477	
T. Bil (mg/dL)	1.	5.6±4.0	4.1±2.4	0.099
	10.	3.6±3.0	2.2±2.2	<0.05
p		0.075	<0.01	
D. Bil. (mg/dL)	1.	0.4±0.7	0.8±1.9	0.058
	10.	0.6±0.4	0.7±0.8	0.169
p		0.213	0.633	
TG (mg/dL)	1.	125.1±75.5	123.7±64.0	0.814
	10.	140.3±78.4	135.6±82.5	0.651
p		0.066	0.198	
T. chol (mg/dL)	1.	109.4±27.2	115.2±32.3	0.491
	10.	121.3±29.5	121.9±31.6	0.944
p		<0.01	<0.05	

D. Bil: Direct bilirubin, T. Bil: Total bilirubin, TG: Triglycerides, T. Chol: Total cholesterol, AST: Aspartate amino transferase, ALT: Alanine amino transferase, SD: Standard deviation.

Table 3. Inflammatory marker levels of groups

		Group 1 (n: 26)	**Group 2 (n: 25)**	
	Days	Median (min-max)	Median (min-max)	p
	1.	4.9 (0.6 – 52)	5.6 (0.7 – 89)	0.545
CRP (mg/L)	4.	4.6 (0.6 – 41)	4.2 (0.6 – 72)	0.706
	7.	4.3 (0.6 – 92)	4.9 (0.6 – 97)	0.671
	10.	5.0 (0.6 – 129)	1.4 (0.6 – 21)	0.564
p		0.946	0.108	
	1.	4.9 (0.1 – 100)	1.6 (0.2 – 100)	0.361
PCT (ng/mL)	4.	0.8 (0.1 – 61)	0.6 (0.1 – 7.9)	0.492
	7.	0.8 (0.1 – 8)	0.5 (0.2 – 2.9)	0.503
	10.	0.5 (0.1 – 12)	0.3 (0.02 – 5)	0.116
p		<0.01	<0.01	
	1.	1.6 (0.3 – 11)	1.7 (0.3 – 6.3)	0.516
NLR	4.	1.6 (0.3 – 17)	2.2 (0.5 – 10.7)	0.828
	7.	1.7 (0.4 – 21)	1.5 (0.6 – 6.1)	0.266
	10.	1.3 (0.5 – 12)	1.4 (0.2 – 11)	0.585
p		0.638	0.158	

CRP: C-Reactive protein, PCT: Procalcitonin, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation.

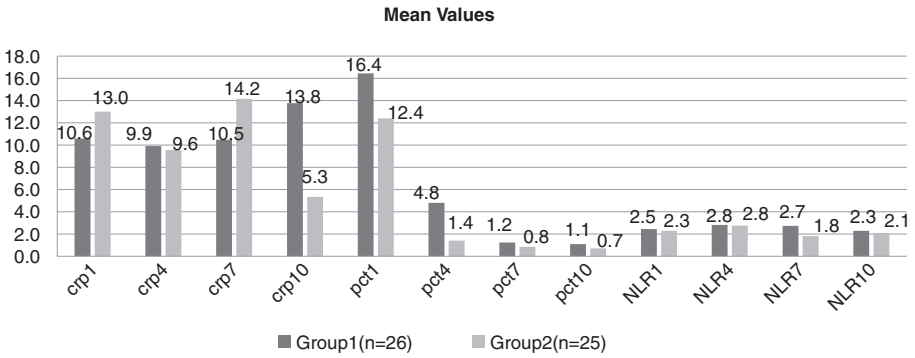

Figure 1. Typical changes of the CRP, PCT, and NLR levels on days 1, 4, 7, and 10 in both groups

a lower phytosterol content than soybean oil. A meta-analysis reviewed 483 preterm infants born before 34 weeks and received TPN under two groups, compared the fish oil group with preterm infants receiving other ILEs, and found no significant difference in body weight, blood bilirubin, TG, and CRP levels, mortality and complications between the two groups [16-18].

In the present study, NLR values were lower in Group 2 (Figure 1). It has been shown that omega-3 fatty acid is found in neutrophil cell membrane phospholipids, where it can be metabolized by neutrophils to ALA metabolites; oxylipins. These metabolites manage functions through various pathways, including neutrophil migration, phagocytic capacity, as well as the production of reactive oxygen species and cytokines. In stress-induced response, neutrophils increase while circulating lymphocytes decrease. An increased neutrophil count indicates increased inflammation, and a low lymphocyte count indicates impaired overall health, resulting in a high NLR. A lower NLR in Group 2 is a positive condition; but the difference is not significant. Compared with other ILEs of fish oil in a preterm animal study; fish oil metabolites increased in cell membrane structure after 11 days. AA has been shown to be present for a longer period of time. Our study covers a period of 10 days. In addition, AA: DHA >1 was found to improve intestinal development. Therefore, the appropriateness of the ratio is important. From this, it is understood that the effect of omega-3 fatty acid on inflammation may be time and dose dependent [19]. In another study, CRP, IL-6, and PCT were significantly lower in the high-dose omega-3 fatty acid group in adult sepsis patients than in the control group [20, 21]. In our study, the follow-up period could have been longer in order to see the clinical results.

CRP, PCT and NLO values of Group 2 decreased in 10 days; CRP increased in Group 1 (Table 3). Furthermore, an intake of 1–2 gr/kg/g is recommended to observe the expected pharmacological effects. However, it is often very difficult to provide such high doses by the parenteral route. The recommended amounts of EPA and DHA for preterm infants are inconsistent. Recent studies indicate that the EPA:DHA ratio and amounts are important [22].The study by Dasilva et al [23]. on animals administered 0.8 mg/kg/week at different EPA:DHA ratios of 1:1, 1:2, and 2:1, and the ratios 1:1 and 2:1 were shown to be more effective in reducing inflammation and oxidative stress. The EPA:DHA ratio of this study was found to be 0.95. Neonates and preterm infants have increased EPA+DHA requirements; high-dose DHA (55–60 mg/kg/g) has been tested and found safe, with better clinical outcomes. On the other hand, a dose of 20 mL/kg/day of 10% fish oil ILE may be required to reach an EPA level of > 40 mg/kg/day. The high dose of EPA in preterm infants did not show any harmful effect, and it was stated that a lower amount of AA might cause growth failure in preterm infants. It was also stated that the inflammatory state might decrease in the long term and pulmonary vasodilation would improve [24]. In addition, clinical recovery was faster in Group 2. It has been ascertained from clinical follow-up records that weight gain was greater, transition time to enteral/

oral feeding was shorter, digestion-absorption were improved, and need for surfactants was less.

In the present study, olive oil-based ILE was used in Group 1. Olive oil does not have a known substrate for prostaglandins or leukotrienes that will affect the immune response, has little or no effect on cellular immune functions, and reduces proinflammatory mediators, adhesion molecules, and cytokines. In general, olive oil has a neutral effect on inflammation, while the risk of oxidative stress and immunosuppression is low [25]. The lack of difference in inflammatory markers between groups (Table 3) may be due to the positive effects of olive oil. Most studies suggest limited differences in relevant laboratory or clinical outcomes or in growth in pediatrics patients receiving different ILEs, although several studies do find benefits from including fish oil or olive oil [26].

After ten days, the NLR value was higher than the predicted reference range in both groups. The normal values of NLR may differ according to age groups, and studies on this subject are quite limited. Aydin et al [27]. Reported the reference range for 0–1 year to be 0.093–1.28 for boys and 0.110–1.86 for girls. In the present study, blood levels of CRP, PCT, and NLR decreased in Group 2 over a ten-day period. In Group 1, blood CRP levels increased and NLR and PCT levels decreased in 10 days (Table 3). In addition, CRP, PCT, and NLR were lower in Group 2 than in Group 1. This may explain the better Group 2 outcomes in response to treatment, recovery period, and alleviation of inflammation. Studies have shown that increased omega-3 derivatives oxilipins due to anti-inflammatory susceptibility resolve inflammation in the host by reducing polymorphonuclear neutrophil infiltration, platelet aggregation and expression of proinflammatory cytokines. Biosynthesis of oxilipins via AA metabolism modulate the host inflammatory response by producing pro- and anti-inflammatory mediators. In the immature preterm infant, the omega-3/omega-6 lipid ratio may affect the immune response to acute inflammation [24, 28-30].

However, the lack of a significant difference in inflammatory markers in the present study makes the situation controversial, as in some studies. For example, a previous review did not find ILE with and without fish oil to be better for preterm infants in preventing cholestasis, growth, mortality, retinopathy, bronchopulmonary dysplasia, and other adverse neonatal outcomes [31]. Once again, it was concluded that the evidence from randomized controlled trials was insufficient to definitively determine whether fish oil ILE provided an advantage in preventing or resolving cholestasis, in another clinical outcome, thus larger and well-designed studies were needed. Another meta-analysis on this subject found that neonates receiving fish oil had a positive modulation in fatty acid profiles and/or decrease in oxidative stress, lipid peroxidation, and cytokine levels compared to other ILEs, meaning that it was effective in regression of inflammation [32]. In a randomized controlled study, 500mL IV soybean was administered to 20 healthy individuals and its effect on lymphocytes and neutrophils 1 hour after the infusion was examined; from the results of the study, 58% of the lymphocytes; It has been shown that 30% of neutrophils are destroyed and it is stated that soybean has a negative effect on the immune system [33]. In another in vitro study, the effects of different doses of soybean oil and olive oil on lymphocytes were examined; olive oil positively affects lymphocyte function and proliferation, albeit at a low level, regardless of the dose; In pedigree, it was shown that lymphocyte function was suppressed as the dose increased [34]. In a study conducted in newborns, it was stated that the NLR value in hypoxic-ischemic encephalopathy may be a determinant of the severity of the immune response to damage and therapeutic intervention [35]. Although omega-6 or arachidonic fatty acids are included in the neutrophil membrane, the presence of omega-3 fatty acids in the medium has been shown to affect neutrophil function. Omega-3 fatty acids and their metabolites modulate neutrophil function in various ways, including neutrophil migration, phagocytic capacity, as well as production of reactive oxygen species and cytokines [36]. Soybean-based omega-6 fatty acid and increased omega-6:omega-3 fatty acid ratio have been shown in studies to increase inflammation and organ damage. It has been stated that mixed lipid emulsions according to omega-6 fatty acids, MCT, olive oil and fish oil based lipid emulsions reduce or improve the incidence of inflammation [37, 38]. In this study, the omega-6:omega-3 ratio of olive oil-based lipid emulsion used for Group 1 was 9:1; for Group 2, this value

was calculated as approximately 2.13 with the addition of fish oil (omega-6:omega-3 ratio 1:8). It is recommended that this ratio should not be more than 4:1 in maintaining health, in the formation of an adequate inflammatory response and in maintaining the pro/anti-inflammatory balance, if possible, it should be 2:1 or 1:1 [39,40]. In a study, it was found that the use of parenteral omega-3 fatty acids in elderly infectious patients significantly reduced NLR compared to the control group. A high NLR is an indicator of poor prognosis [41]. In this study, although inflammation markers were at lower levels in the fish oil group, only olive oil-based lipid emulsion was used in the other group. The lack of significant difference in inflammation markers between groups may be due to the use of olive oil-based lipid as the main lipid solution. Significant reduction in the results of some liver function tests, lower levels of inflammatory markers in the fish oil group, and improved clinical outcomes indicate that the addition of omega-3 fatty acids to TPN therapy may have a positive effect. There are no clear data on the use of fish oil for the prevention/treatment of cholestasis, suppression of systemic inflammation, and the association reflection on clinical outcomes. Most of the uncertainties are about the usage amounts of omega-3 fatty acids and EPA/DHA. There are concerns about the distribution, type, and amount of lipid profile to be used should fish oil be used to prevent or treat complications is uncertain [42]. According to these findings, uncertainties remain in the treatment period, effective dose, and ratio of fatty acids for fish oil and other fatty acids.

Conclusion

Fatty acids are essential for neonates. Studies on its use in disease settings are insufficient. Most of the studies used ILEs that combined all fatty acids. Although the positive effects of omega-3 fatty acids and EPA/DHA are known; There is uncertainty about how long the amount and duration should be. The present study established a low level of positive changes in inflammatory findings and a decrease in liver function test results with the addition of fish oil to TPN. The different fatty acid contents of ILEs, the optimum ratio between the fatty acids, and the amount and duration of use affect the clinical outcomes.

No potential conflict of interest relevant to this article was reported by the authors.

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