Are Three Different Lipid Combinations Effective on The Immune System in Sepsis Patients?

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Abstract

Aim: We aimed to analyze the effect of the 3 different parenteral nutrition's (MCT/LCT (long and medium chain fatty acids), LCT with omega-9 (ω-9) and MCT/LCT with ω-3 and ω-9 on the inflammatory cytokine levels in sepsis patients. This is the first study from the Southern part of Turkey.

Methods: We included 30 patients, diagnosed with sepsis and took total parenteral nutrition in this study. Patients were divided into 3 randomized groups in terms of what parenteral nutrition have been taken. (Group A, B and C) Blood samples were taken and TNF-α, IL-1, IL-6 and IL-8 levels were evaluated. Adverse effects were recorded. TNF-α, IL-1β, IL-6, and IL-8 levels of were analyzed by ELISA method and each sample were studied in duplicate.

Results: The median age of the patients included in the study was 52 and 24 (80%) of them were male. The SOFA score was 5 in study group. We examined IL-1, IL-6, IL-8 and TNF-α distribution on the day of the first, third and fifth days depending on time. The inflammatory cytokine levels were not found statistically significant ($p > 0.05$) when we compared the study groups via 3 different parenteral nutrition's.

Conclusions: When we compare MCT/LCT, LCT/ω-9 and MCT/LCT, ω-3, ω-9 which are given as a component of total parenteral nutrition we concluded that there was no superiority to others in terms of proinflammatory cytokine levels in sepsis and they didn't increase proinflammatory cytokines. There is a need for more randomized controlled studies investigating the effect of lipids on the course of the disease in sepsis patients who cannot receive enteral nutrition and require TPN support.

Keywords: *Sepsis, lipid, cytokine*

1. Introduction

Sepsis is one of the most serious problems encountered in intensive care units; moreover, it causes hospitalization and is a complication occurring during hospitalization. Despite all supportive treatments and use of strong antibiotics, it results in 30%–70% mortality and significantly reduces the quality of life among sepsis survivors[1, 2]. Sepsis is defined as the uncontrolled systemic inflammatory response of the host to infection. Notably, it is caused when the causative microorganism interacts with the host's immune, inflammatory, and coagulation responses. In other words, both host response and causative microorganism are responsible for sepsis[3]. The physiopathological events occurring during sepsis are complex.

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Many antigenic structures and toxins in the bacterial cell wall trigger the release of several potent mediators from circulating mononuclear phagocytes, endothelial cells, and other cells. These mediators particularly include tumor necrosis factor alpha (TNF-α); interleukins 1, 2, 6, and 8 (IL-1, IL-2, IL-6, and IL-8); and platelet-activating factor (PAF)[4]. In patients with sepsis, total parenteral nutrition (TPN) is used to provide nutrition as well as to reduce the metabolic response to stress, positively control the immune system, and enhance clinical findings[5].

Intravenous lipid emulsion (IVFE)—a crucial element of TPN—is rich in essential fatty acids and is an energy-dense source of calories. Notably, lipid emulsions comprise many bioactive components, including fatty acids[6]. Further, various fatty acids can have different effects on several physiological processes, such as injury healing, metabolism, blood coagulation, oxidative stress, cell and organ functions and multiplication, inflammation, and immune response[7]. Conventionally, IVLE were composed of soybean oil (SO)[8, 9]. Nevertheless, SO is rich in ω-6 polyunsaturated long-chain triglycerides (LCT) which may contribute to immunosuppression in sepsis cases as relevant evidence has suggested. Moreover, SO may contribute to increased risk of complications by exacerbating the release of

proinflammatory cytokines and prostaglandin 2[10, 11]. Therefore, novel strategies have been developed to reduce the LCT content in parenteral nutrition lipid emulsions using other fats, such as medium-chain fatty acids (MCT), ω-9 containing olive oil (OO), or ω-3 containing fish oil (FO)[12].

This study aimed to compare three different lipid emulsions (those containing MCT/LCT; LCT and ω-9; or MCT/LCT, ω-3, and ω-9) in patients who diagnosed with sepsis,

These emulsions were employed in the TPN given to the patients to determine their effects on the levels of proinflammatory cytokines such TNF-, IL-1, IL-6, and IL-8 and to find out if any of them were better than the others.

2. Materials and methods

The present study was performed on patients in the intensive care unit (ICU) of Çukurova University School of Medicine Training and Research Hospital during a 13-month period between March 2015 and April 2016. This study received ethics approval from Çukurova University School of Medicine Ethics Committee (date: 19/03/2015; approval number: 39/11).

2.1. Selection of Patients

After ethics committee approval and informed consent from the patients or their caregivers were obtained, 37 patients (age > 18 years) who were diagnosed with sepsis and receiving TPN support were enrolled. Seven patients were excluded from the study: five patients in the experimental group were excluded owing to the transition to enteral nutrition, and two patients were excluded owing to the progress to septic shock. The diagnosis of sepsis was based on the focus of infection and the Sequential Organ Failure Assessment (SOFA > 2) criteria. Exclusion criteria were as follows: patients aged ≤18 years, those who were pregnant, those who had severe sepsis and septic shock, those who received corticosteroids (≥1 mg/kg) within the last 48 hours, those who were receiving major immunosuppressive drugs, those who tested positive for HIV, those who had a plasma triglyceride concentration of >200 mg/dL, those who had severe hyperglycemia (glucose >250 mg/dL), those who had acute kidney injury following the Kidney Disease Improving Outcomes guideline criteria, those who had fatal disease, and those who were able to receive enteral nutrition. The daily lipid profiles of the patients were followed and the patient was excluded from the study when the study limits were exceeded in triglyceride and other lipid values.

2.2. Nutritional Regiments Delivered to Patients

Participants were grouped into three in a random pattern, based on the parenteral nutrition composition using the website www.randomizer.org as follows:

Group A (n=10); TPN containing 1 g/kg MCT/LCT (Nutriflex®)

Group B (n=10); TPN containing 1 g/kg LCT and ω-9 (Oliclinomel N7®)

Group C (n=10); TPN containing 1 g/kg MCT/LCT, ω-3, and ω-9 (SMOF Kabiven®)

All patients were fed via a central venous catheter for 5 days. All groups received nutrition with 4 g/kg of glucose and 2 g/kg of protein administered as infusion for 24 hours. Based on the guidelines provided by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), we computed the required energy (total energy: 25–30 kcal/kg/day; protein: 1.2–2 g/kg/day)[13-15]. The target calorie intake was reached on day 4. The patients started receiving enteral nutrition in accordance with the hospital and enteral nutrition protocols based on daily examinations by the ICU physician and dietician.

2.3. Collection of Samples

The day the patients started to receive nutrition was defined as day 0. The age, gender, height, and weight of all patients were recorded (Table 1). Blood samples of the patients included in the study were collected between 08:00 and 10:00 in the morning on days 0, 3, and 5. Approximately 5 mL of whole blood from each patient was taken into gel separation tubes (BD Vacutainer® SST™ II Advance). The plasma of all samples was then separated by centrifugation at 1,500xg for 10 minutes at 4 °C and stored at –80 °C until experimental studies were performed. Allergic reactions, fever, and side effects were documented in all patients included in the study.

2.4. ELISA Assay

All samples were allowed to reach room temperature before the proinflammatory parameters were determined by ELISA and TNF-α, IL-1β, IL-6, and IL-8 levels of each sample were analyzed in dublicate.

IL-1β levels of the samples were obtained using ELISA kit (Human IL-1β; Catalogue number: KAP1211; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human IL-1β ELISA kit was 0-13.6 pg/mL, detection limit 0.35 pg/mL, intra-assay CV <2.3%, inter-assay CV <4.5%, and accuracy 90-97%.

IL-6 levels of the samples were obtained using ELISA kit (Human IL-6; Catalogue number: KAP1261; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human IL-6 ELISA kit was 0-17 pg/mL, detection limit 2 pg/mL, intra-assay CV <4.2%, inter-assay CV <4.4%, and accuracy 97-102%.

IL-8 levels of the samples were obtained using ELISA kit (Human IL-8; Catalogue number: KAP1301; DIAsource®, Belgium;) according to the manufacturer's instructions. The measurement range of the Human IL-8 ELISA kit was 0-50 pg/mL, detection limit 1.1 pg/mL, intra-assay CV <3.2%, inter-assay CV <8.6%, and accuracy 105-119%.

TNF-α levels of the samples were obtained using ELISA kit (Human TNF-α; Catalogue number: KAP1751; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human TNF-α ELISA kit was 4.6–12.4 pg/mL, detection limit 0.7 pg/mL, intra-assay CV <6.6%, inter-assay CV <4.5%, and accuracy 91–100%.

2.5. Statistical Method

We conducted the statistical analysis of all information through SPSS 17.0 software. Categorical variables were shown numerically and in ratio, whereas continuous variables were presented as mean ± standard deviation (minimum, maximum, and median if needed). We evaluated how the data is distributed when continuous variables are compared among the groups, and applied the Kruskal–Wallis and Mann–Whitney U tests because the prerequisite of parametric distribution was not met. The results of the time-dependent test were compared using the Wilcoxon test and repeated-measures ANOVA. Significance was met when p-value < 0.05 for all tests.

3. Results

3.1. Demographic Characteristics

The 30 participants have a median age of 52 (19–81) years; of these, 80% (n=24) patients were men. The mean body mass index (BMI) of the patients was 25.1±3.3 kg/cm^2. The median SOFA score was 5 (4–9). Demographic characteristics of the patient groups were similar. The three groups did not significantly differ regarding age, height, BMI, and SOFA scores (Table I).

3.2. IL-1β Measurements

The groups did not significantly change when analyzing the median IL-1β levels at baseline and on days 3 and 5. Moreover, time-dependent variations within the groups were not statistically

different (Table II). The measurement of IL-1β on day 0 revealed the median levels of 0.02 (0.01–7.76), 0.02 (0.01–2.94), and 0.45 (0.01–22.1) pg/mL in the three groups (A, B, and C), respectively (p >0.05). Similarly, the median IL-1β on day 3 were 0.02 (0.01–0.93), 0.11 (0.01–161.4), and 0.54 (0.01–72.2) pg/mL in the three groups, respectively (p >0.05). As for the levels on day 5, they were 0.03 (0.01–17.7), 0.02 (0.01–39.7), and 0.66 (0.01–16.7) pg/mL in the three groups, respectively (p >0.05).

Table 1

Distribution of Demographic Characteristics

	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
Age (years)	49 (20–68)	53 (19–81)	54 (19–63)	>0.05
Weight (kg)	80 (50–92)	77 (49–82)	77 (57–87)	>0.05
Height (m)	1.75 (1.52–1.87)	1.72 (1.63–1.78)	1.73 (1.64–1.81)	>0.05
BMI (kg/m²)	26.4 (21.5–28.1)	25.5 (18–30.1)	25.8 (19.5–32.4)	>0.05
SOFA score	5 (4–8)	5 (4–9)	6 (4–9)	>0.05

Table 2

Distribution of IL-1β Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-1β (pg/ml)	0	0.02 (0.01–7.76)	0.02 (0.01–2.94)	0.45 (0.01–22.1)	>0.05
	3	0.02 (0.01–0.93)	0.11 (0.01–161.4)	0.54 (0.01–77.2)	>0.05
	5	0.03 (0.01–17.7)	0.02 (0.01–39.7)	0.66 (0.01–16.7)	>0.05

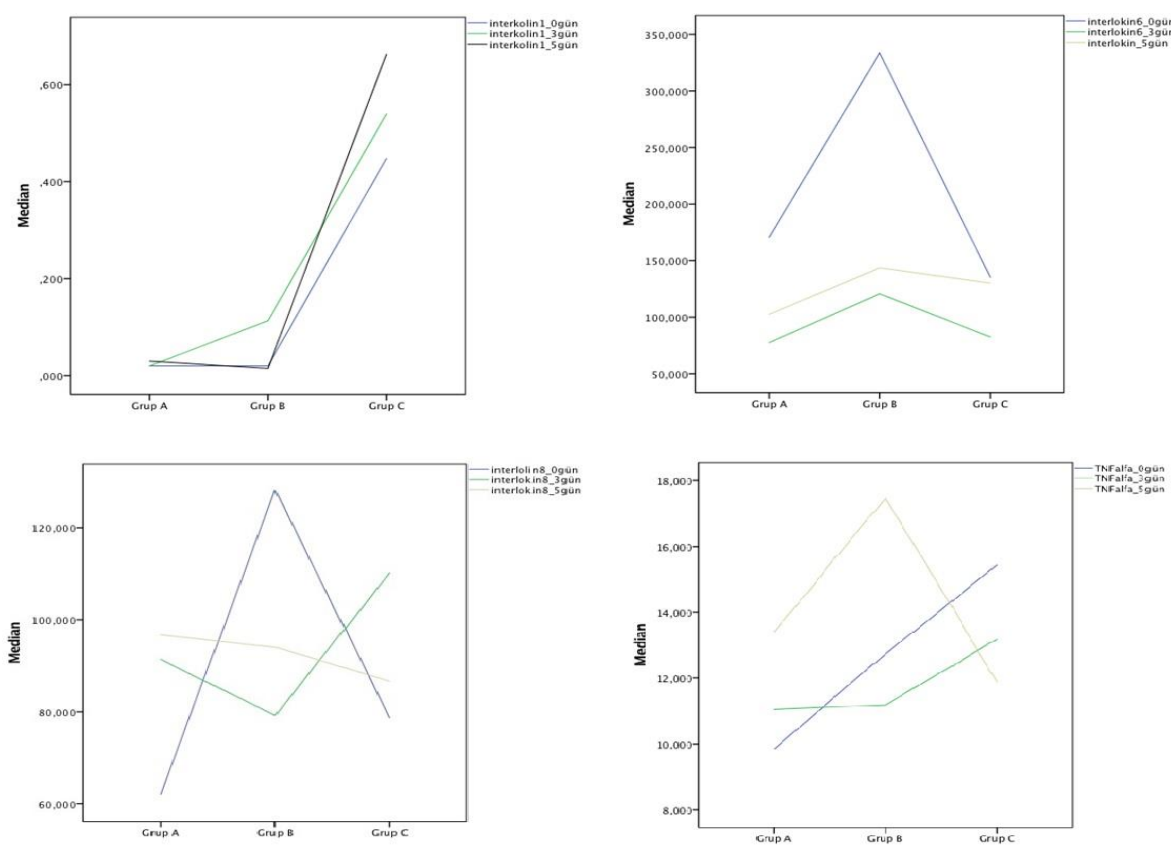
Figure 1 shows the distribution of IL-1β level at days 0, 3, and 5 as well as the time-dependent changes for each group. Although the levels comparatively increased and decreased in all three groups, the increase was most evident in the Group C, but the analysis of changes over time in terms of groups revealed no significant difference (Figure 1).

3.3. IL-6 Measurements

Analysis of median IL-6 levels at days 0, 3, and 5 did not significantly changed among the three groups. Moreover, time-dependent variations within the groups were not statistically different (Table III).

Figure 1

Comparison of proinflammatory cytokine levels of the groups



Median IL-6 levels on day 0 were 170.6 (15.5–546.7), 333.6 (46.4–1821.4), and 135.3 (50.1–761.2) pg/mL in the three groups (A, B, and C), respectively (p >0.05). The levels on day 3 were 77.6 (10.7–256.9), 120.7 (32.4–659.1), and 82.5 (26.9–942.3) pg/mL in the three groups, respectively (p >0.05). Further, the levels on day 5 were 102.6 (32.2–337.7), 143.6 (56.5–347.2), and 130.2 (37.6–1709) pg/mL in the three groups, respectively (p >0.05).

Table 3

Distribution of IL-6 Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-6 (pg/mL)	0	170.6 (15.52–546.7)	333.6 (46.42–1821.4)	135.3 (50.13–761.2)	>0.05
	3	77.6 (10.75–256.9)	120.7 (32.4–659.1)	82.5 (26.94–942.3)	>0.05
	5	102.6 (32.18–337.7)	143.6 (56.49–347.2)	130.2 (37.6–1709)	>0.05

Figure 1 presents the distribution of IL-6 level at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. None of the three groups demonstrated consistent increase or decrease in these levels. Moreover, the analysis of changes in measurements over time for these groups revealed no statistically significant difference (Figure 1).

3.4. IL-8 Measurements

Analysis of median IL-8 levels at days 0, 3, and 5 revealed a negative significant difference between the groups. Moreover, time-dependent changes within the groups showed no statistical difference (Table IV). Median IL-8 levels at baseline were 62.0 (32.8–664.6), 128.1 (37.8–913.1), and 78.7 (13.7–645.3) pg/mL in the three groups (A, B, and C), respectively (p >0.05). The levels on day 3 were 91.4 (46.8–280.3), 79.2 (40.5–1283.2), and 110.2 (48.2–865.4) pg/mL in the three groups, respectively (p >0.05). Further, the levels on day 5 was 96.8 (42.8–738.7), 94.1 (29.2–633.2), and 86.7 (42.3–1280.5) pg/mL in the three groups, respectively (p >0.05).

Table 4

Distribution of IL-8 Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-8 (pg/mL)	0	62.0 (32.81–664.6)	128.1 (37.83–913.1)	78.7 (13.68–645.3)	>0.05
	3	91.4 (46.8–280.3)	79.2 (40.52–1283.2)	110.2 (48.2–865.4)	>0.05
	5	96.8 (42.76–738.7)	94.1 (29.25–633.2)	86.7 (42.31–1280.5)	>0.05

Figure 1 shows the distribution of IL-8 levels at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. The Group A seemed to demonstrate a consistent increase in this level, whereas the other groups had both increases and decreases, but the analysis of changes in the measurements over time for these groups revealed no statistically significant difference (Figure 1).

3.5. TNF-α Measurements

The three groups did not significantly differ when testing the median TNF-α levels at days 0, 3, and 5. Moreover, time-dependent changes within the groups were not statistically significantly different (Table V). Median and range TNF-α levels at baseline were not significantly different between the three groups (9.8 (2.9-17.2), 12.7 (5.1-35.1), and 15.4 (4.0-102.6)) pg/mL, respectively] (p >0.05).Similar results between the groups were obtained at days 3 and 5 (11.1 (4.7–24.7), 11.2 (6.6–29.1), and 13.2 (6.0–51.9)) and (13.4 (5.5–27.8), 17.5 (4.0–30.5), and 11.9 (6.1–43.9)), respectively (p >0.05).

Table 5

Distribution of TNF-α Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
TNF-α	0	9.8 (2.92–17.2)	12.7 (5.11–35.1)	15.4 (4.04–102.6)	>0.05
	3	11.1 (4.72–24.7)	11.2 (6.60–29.1)	13.2 (6.02–51.87)	>0.05
	5	13.4 (5.47–27.8)	17.5 (4.0–30.5)	11.9 (6.13–43.93)	>0.05

Figure 1 shows the distribution of TNF-α levels at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. Although there was a consistent increase these levels in the Group A and a consistent decrease in the Group C, analysis of the changes in measurements over time for these groups revealed no statistically significant difference; this may be attributed to the limited number of patients and randomized inclusion of the patients (Figure 1).

3.6. Adverse Effects

None of the groups experienced any allergic reaction to the nutritional mixtures.

4. Discussion

The lipid content of TPN in patients with sepsis has gained increased importance after it was reported to have effects on eicosanoid metabolism and the levels of proinflammatory cytokines. Recent studies have stated that the use of SO-based lipids may cause an increase in the levels of potentially harmful prostaglandins in sepsis owing to their ω-6 content[10, 11, 16, 17]. Briefly, it was found in this study that three different TPN mixtures, grouped MCT/LCT; LCT with ω-9; and MCT/LCT with ω-3 and ω-9, did not lead to any differences in proinflammatory cytokine levels in patients with sepsis. Since there hasn't been comparative research of these three lipid combinations, we believe that this is an important contribution to the field.

Dominique Granado et al. compared the effects of nutritional emulsions with SO- and OO-based lipid compositions on immune functions in human cells in vitro. They reported that SO-containing emulsions inhibit lymphocyte proliferation, whereas OO-containing emulsions do not. Moreover, both emulsions tended to inhibit the release of TNF-α and IL-1β to a similar extent[18]. In our study, we could not see any change in IL-1β level in group B containing FO, while an increase in TNF-α level was observed. In a double-blind randomized study of 32 infants undergoing open heart surgery, Larsen et al. compared pure SO-based lipids with emulsions containing 40% MCT, 50% LCT, and 10% FO. They evaluated TNF-α, IFN-γ, GM-CSF, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, and IL-10 levels at four days, i.e., at 2 hours before surgery as well as at 24 hours, 7 days, and 10 days after surgery. They found that TNF-α levels were

lower in the FO group at 24 hours after surgery[19]. In our study, we observed an increase in TNF-α level in group B containing FO. Owing to the randomized selection of patients and the complexity of the pathogenesis of sepsis, this conclusion can be attributed to the small number of patients. Further, Konstantin Mayer et al. investigated whether parenteral nutrition comprising ω-3 and ω-6 affected proinflammatory cytokine levels in 21 patients with sepsis. They found a decrease in cytokine levels in the ω-3 group, but there was a significant rise in proinflammatory cytokine levels in the ω-6 group[20]. However, in the present study, we did not use any SO-based emulsions containing ω-6 owing to their potentially harmful effects on proinflammatory cytokine levels in patients with sepsis. For this reason, we used TPN products containing other different lipid mixtures used to reduce LCT/ ω -6 level in our study.

Ming-Hsun Wu et al. investigated the effects of parenteral nutrition containing MCT/LCT, ω-3, and ω-9 and those containing only MCT/LCT on inflammatory markers in patients undergoing gastrointestinal surgery. They evaluated IL-6, CRP, TNF-α, and TGF-1β levels to be insignificantly changed between the two groups[21]. We could not find a statistically significant difference between the two groups in our findings. We attributed this to the difference between the pathogenesis of sepsis and the inflammatory response secondary to surgery. Maria Skouroliakou et al. studied the difference between the effects of parenteral emulsions containing MCT/LCT-, ω-3, and ω-9-based lipids with those of emulsions containing ω-6-based lipids alone on inflammatory cytokines in 60 infants. IL-6 and IL-8 levels were not significantly different between the two groups when compared to TNF-α levels, although they showed to be less in patients receiving mixed lipid content[22]. Stanislaw Klek et al. administered parenteral nutrition containing MCT, ω-6, ω-3, and ω-9 lipids as well as emulsions with SO-based lipids alone to 73 intestinal failure patients for 4 weeks and compared IL-6, sTNF-RII, and CRP levels between the two groups. The results of their clinical trial revealed no difference between the two groups[23]. Different results can be expected from the sepsis patient group in our study, since there is some impairment in lipid absorption, albeit at different rates, in patient groups with intestinal insufficiency. Veronique Donoghue et al. conducted a randomized controlled trial to investigate parenteral nutrition comprising MCT/LCT, ω-3, ω-9, and ω-6 in 68 patients. They reported that TNF-α concentrations declined from day 1 to day 6 in the groups that received parenteral nutrition emulsions containing MCT/LCT, ω-3, ω-9, and ω-6, whereas it increased in the group that received soy-based parenteral nutrition emulsions; however, the difference was not statistically significant[24]. The present study compared between parenteral nutrition containing MCT/LCT, ω-3, and ω-9 and only MCT/LCT; no significant difference was detected between the two groups in terms of proinflammatory cytokine levels. We attributed this result to the use of mixtures where the LCT content was similarly reduced to 50%.

In a clinical study of 32 patients, Gültekin et al. compared parenteral nutrition emulsions containing ω-9 lipids with those containing ω-3 lipids in patients with critical sepsis and septic shock. They evaluated IL-6 and TNF-α levels on days 1 and 6, but no significant difference between the two groups was detected[25]. Moreover, Jean-Marie Reiumund et al. investigated the effects of parenteral nutrition with LCT, MCT/LCT, and 80% OO-based lipids on inflammatory cytokine levels in vitro. They found that parenteral nutrition regimens containing OO-based lipids triggered the release of TNF-α and IL-1β to a lesser extent but did not lead to a significant difference in IL-6 and IL-8 concentrations[26]. In a randomized double-blind study of 100 patients at ICU, Umpierrez et al. administered emulsions containing pure SO-based and OO-based lipids for 28 days and evaluated TNF-α, CRP, and IL-6 levels in both groups. They found no significant difference between the two groups[27]. Agnieszka Gawechka et al. administered a parenteral nutrition emulsion containing SO-based lipids and a parenteral emulsion containing ω-9 lipids for 14 days to 38 premature infants and compared the emulsions in terms of their effects on inflammatory cytokines. However, their study failed to demonstrate any statistically significant change among the two groups regarding TNF-α, IL-6, and IL-10 levels[28]. Although we included only sepsis patients in our study, we could not find a similarly significant difference. Ulusoy et al. compared a parenteral emulsion containing ω-6 lipids with another parenteral emulsion containing ω-9 lipids administered for 10 days to 40 patients with sepsis and investigated the effects of these emulsions on inflammatory cytokines. They found a decrease in IL-1β, IL-6, IL-10, and TNF-α levels in all patients regardless of lipid solutions, but they failed to report any significant difference in terms of lipid content[29]. The present study reported that lipid emulsions containing ω-9 did not lead to a significant difference in proinflammatory cytokines in patients with sepsis compared to emulsions containing MCT/LCT lipids and those containing MCT/LCT, ω-3, and ω-9 lipids. We think that reducing the LCT ratio, which is the main source of proinflammatory cytokines, to 50% or less will lead to similar results.

In contrast to the present study, some previous reports have indicated that certain lipids alter proinflammatory cytokine levels. Hsiao et al. compared a parenteral emulsion containing MCT/LCT with a parenteral emulsion containing MCT/LCT, ω-3, and ω-9 (30%, 30%, 25%, 25%, 15%) used for 7 days in 60 premature infants and examined their effects on inflammatory cytokines. IL-1 and IL-6 levels were significantly reduced in the group that received the emulsion containing MCT/LCT, ω-3, and ω-9[30]. Our results may have been different because the lipid mixture ratios in the solution we used in our study were different from the mixture used here. Sungurtekin et al. administered a parenteral emulsion containing MCT/LCT lipids and another parenteral emulsion containing ω-3 lipids for 10 days in 40 patients with sepsis and SIRS. They found that TNF-α and IL-6 levels on day 7 were significantly higher in patients with sepsis who received the emulsion containing MCT/LCT lipids compared to those who received the emulsion containing ω-3 lipids. In contrast, IL-1 levels were found greater in the MCT/LCT group than in the ω-3 group on days 3, 7, and 10. Similarly, IL-10 levels in the ω-3 group were above the MCT/LCT group on days 3 and 7[31]. Since we ended our study on the 5th day, we did not find any significant difference between the groups. Barbosa et al. compared parenteral nutrition containing MCT/LCT (50%/50%) lipids with parenteral nutrition containing MCT/LCT/ω-3 (40%/50%10%) lipids in a study of 25 patients with sepsis and SIRS. Their clinical study compared IL-1β, IL-6, IL-10, and TNF-α levels between the two groups and found a significant decrease on day 5 in IL-6 and IL-10 levels in the group that received the emulsion containing FO[32]. Failure to find a significant difference in the three different lipids in this study might be attributed to the small sample of participants.
Consistent with the results of the present study, the current guidelines and reviews do not provide any recommendation on lipid selection. Additionally, the most recent guidelines published by the ASPEN do not recommend any particular formulation as there is no clear evidence of the superiority of any particular lipid in parenteral nutrition[33]. Similarly, the Metabolism and Nutrition Working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units recommend that the use of mixed formulas that lower the ω-6/ω-3 ratio for lipid selection is useful as a pharmacological strategy for artificial nutrition. However, they did not recommend a lipid of choice for critically ill patients[34]. A review by Abbasoglu et al. compared the effects of ω-3-containing parenteral nutrition emulsions with other lipid emulsions and reported different effects on inflammatory cytokines, but they did not report a significant superiority of any specific lipid over others[35].

This study has several limitations. First, patients could not be followed up after day 5. Second, the sample of participants was relatively small. Third, the total number of days during which the patients received TPN was not analyzed. These limitations warrant randomized controlled trials with greater number of patients and lengthier times of follow-up.

5. Conclusion

Most lipids that are used for nutritional purposes are immunoregulatory substrates with a major depressive effect. Sepsis is associated with high morbidity and affects the immune system as well as leads to excessive inflammatory responses. There are still not enough randomized controlled studies examining how lipids affect the course of the disease in sepsis patients who need TPN treatment but cannot obtain enteral nutrition.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Cukurova University* Scientific Research and Publication protocol number 2015-39/11

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Thesis number 435538
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=cbOXH84ZayrLjc0tI-QXKi75hCcgEI7Dj1ZmFUXXmCeP3V3YTq0LBgMmv8Qd2tKv

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