Effect of changing the lipid component of home parenteral nutrition in adults

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Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; GGT, gamma-glutamyltranspeptidase; HPN, home parenteral nutrition; IFN, interferon; IL, interleukin; LE, lipid emulsion; PC, phosphatidylcholine; PN, parenteral nutrition; PUFA, polyunsaturated fatty acid; TNF, tumour necrosis factor.

Abstract

Background: The effect of different lipid emulsions (LEs) within the parenteral nutrition (PN) regimen of adult home PN (HPN) patients is not clear. This study investigated the effect of changing adult HPN patients from a soybean oil based LE (Intralipid) to either a fish oil containing LE (providing n-3 fatty acids) (SMOFLipid) or an olive oil based LE (ClinOleic).

Methods: 32 adults receiving long-term HPN with Intralipid as the LE were transferred to receive either SMOFLipid (n = 13) or ClinOleic (n = 19) for 60 days. Liver function markers, cholesterol, triglycerides, a full profile of fatty acids, and several cytokines were measured at study entry and after 60 days.

Results: SMOFLipid did not affect liver function markers, blood lipids or plasma cytokines. ClinOleic lowered both gamma-glutamyltranspeptidase (P = 0.044) and interleukin-8 (P = 0.030) concentrations. Both LEs induced marked changes in the fatty acid profile of plasma. SMOFLipid resulted in significant decreases in the proportions of linoleic acid, several other n-6 fatty acids and the essential fatty acid (EFA) deficiency indicator mead acid and significant increases in the proportions of the n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. ClinOleic resulted in significant decreases in the proportions of some saturated fatty acids, linoleic acid, several n-6 fatty acids, all n-3 fatty acids and mead acid and a significant increase in the proportion of oleic acid. The ratio of mead to arachidonic acid in plasma was not altered by either SMOFLipid or ClinOleic. No patient had a mead acid to arachidonic acid ratio of > 0.2, the cut-off used to indicate EFA deficiency.

Conclusion: Both SMOFLipid and ClinOleic significantly alter the fatty acid profile of plasma in adult HPN patients previously using Intralipid. Neither LE induces EFA deficiency in these patients. SMOFLipid did not alter liver function markers or inflammation. In contrast, ClinOleic decreased some, though not all, markers of liver function and inflammation. SMOFLipid and ClinOleic may both be considered for use in adult HPN patients.

Introduction

Home parenteral nutrition (HPN) is an established therapy that aims to provide adequate amounts of amino acids, glucose, lipids, electrolytes and water in order to prevent malnutrition in patients requiring long-term parenteral nutrition (PN) due to prolonged gastrointestinal tract failure [1-3]. The traditional source of lipid in HPN has been emulsifed soybean oil. Soybean oil is rich in the n-6 polyunsaturated fatty acid (PUFA) linoleic acid (18:2n-6) which comprises about 50% of the fatty acids present [4]. Linoleic acid is an essential fatty acid (EFA). The other EFA is the n-3 PUFA α-linolenic acid (18:3n-3), which comprises about 7% of fatty acids in soybean oil [4]. Thus, soybean oil is a good source of EFAs. However, it is considered that soybean oil increases the risk of liver disease (i.e. intestinal failure associated liver disease) either because of its high linoleic acid content or its high phytosterol content [5]. Linoleic and α-linolenic acids are metabolised to longer chain, more unsaturated bioactive derivatives arachidonic acid (20:4n-6) and eicosapentaenoic acid (EPA; 20:5n-3) respectively. EPA can be further metabolised to docosahexaenoic acid (DHA; 22:6n-3), although it is considered that this conversion is limited in humans [6]. Arachidonic acid, EPA and DHA have many physiological roles and actions and act to control hepatic metabolism, blood lipid concentrations, inflammation, immune responses, cardiac function and blood clotting, amongst others [7]. In general, arachidonic acid and the two n-3 PUFAs EPA and DHA act in opposition to one another. This is very well described for inflammation where, in general, arachidonic acid has pro-inflammatory roles while EPA and DHA are anti-inflammatory and inflammation resolving [8,9]. It has been proposed that soybean oil, with its preponderance of linoleic acid, might act to promote inflammation by providing substrate for synthesis of arachidonic acid; furthermore linoleic acid itself gives rise to pro-inflammatory chemical mediators [10]. Hence, lipid emulsions with reduced soybean oil content have been developed for use in parenteral nutrition [4,11].

ClinOleic (Baxter Healthcare) is an 80:20 (vol/vol) mixture of olive oil and soybean oil. The linoleic acid content is about 20% of fatty acids and the most prevalent fatty acid is oleic acid (18:1n-9) which comprises about 60% of fatty acids [4]. α-Linolenic acid comprises about 3% of fatty acids in ClinOleic [4]. SMOFLipid (Fresenius Kabi) is a 30:30:25:15 (vol/vol/vol/vol) mixture of soybean oil, medium-chain triglyceride rich oil, olive oil and fish oil. Fish oil is a source of EPA and DHA. Linoleic and α-linolenic acids comprise about 20 and 2% of fatty acids in SMOFLipid, respectively [4], while EPA and DHA together comprise about 5% [4]. Thus, both ClinOleic and SMOFLipid have a decreased content of linoleic acid compared with soybean oil and so they may avoid the proposed deleterious consequences of too much n-6 PUFA [4]. Furthermore, SMOFLipid provides the health promoting long chain n-3 PUFAs EPA and DHA. Thus, both ClinOleic and SMOFLipid could be of benefit in patients on HPN. However, there is a concern that the more limited supply of linoleic and α-linolenic acids with these newer lipid emulsions could lead to EFA deficiency. The biochemical sign of EFA deficiency is increased content of mead acid (20:3n-9) which is produced from oleic acid when insufficient EFAs are available for metabolism [12], and often this is expressed as the ratio of mead acid to arachidonic acid [13].

Despite the availability of ClinOleic and SMOFLipid in many countries for a number of years, there are limited data on their use in adult patients in the home-care setting [14] and there are few head-to-head comparisons. Therefore, the current study compared the effect of changing the lipid emulsion used by adults on long term HPN from Intralipid (Fresenius Kabi), which is emulsified soybean oil, to either ClinOleic or SMOFLipid. The duration of the intervention was 60 days and the outcomes assessed related to liver function, blood lipids, fatty acids including the marker of EFA deficiency, and inflammation.

Materials and Methods

Study design and patient population

This was a prospective, comparative study with 2 parallel groups conducted at two Polish parenteral nutrition centers (Warsaw and Łódź) from January 2016 to September 2016. The study protocol and informed consent form were approved by the Bioethical Committee of Warsaw Medical University. Written informed consent was obtained from all participating patients.

32 stable adult patients with intestinal failure supported by HPN (19 women and 13 men; mean age 58 years) were recruited into the study. Patient inclusion criteria were: duration of HPN a minimum of 2 years prior to the study, PN provided as 7 infusions per week; being part of the hospital's HPN programme, and oral feeding and drug therapy unchanged during the 2 months prior to inclusion in study. Exclusion criteria were: active infection, or liver or renal failure or both. All patients had been receiving Intralipid 20% (Fresenius Kabi, Bad Homburg, Germany) as part of their PN support prior to study entry. This was changed to SMOFLipid 20% (Fresenius Kabi, Bad Homburg, Germany) for n = 13 patients in Warsaw or to ClinOleic 20% (Baxter SAS, Maurepas-Cedex, France) for n = 19 patients in Łódź. Patients received the same amount of lipid before and after the change of lipid emulsion.

Blood samples were collected 7 days prior to and again 60 days after changing lipid emulsion. These two time points are referred to as t_{START} and t_{END}.

Blood processing and overview of analyses performed

Blood was collected into disodium-EDTA as anti-coagulant. An aliquot was used for routine biochemical analyses. The following were measured: total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), total cholesterol and total triglycerides; both sites used the same methodologies for these analyses although different cut-offs are used at the two sites for the normal ranges. An aliquot of blood

was immediately centrifuged and plasma was isolated; this was stored at -80°C until analysis. The following were measured in plasma: cytokines including interleukin (IL)-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α and fatty acids in total plasma and in plasma phosphatidylcholine (PC).

Measurement of fatty acids in plasma and plasma PC

Lipid was extracted from plasma using 5 ml of chloroform: methanol (2:1; vol/vol) containing 0.2 M butylated hydroxytoluene as antioxidant. Sodium chloride (1 M; 1 mL) was added and the sample vortexed and then centrifuged. The lower solvent phase was aspirated and evaporated to dryness under nitrogen at 40°C. The total lipid extract was divided into two, with one half retained for analysis of fatty acids in total plasma lipid and the other half used for analysis of fatty acids in plasma PC. The latter was isolated from the plasma lipid extract using solid phase extraction on NH_2 cartridges (Agilent). PC was eluted from the cartridges with chloroform: methanol (60:40 v/v) and evaporated to dryness under nitrogen at 40°C. For both the total lipid extract and the PC, fatty acids were removed and simultaneously derivatized to methyl esters by incubation with 1 mL 2% H_2SO_4 (vol/vol) in methanol for a minimum of 2 hours at 50^{o}C to form fatty acid methyl esters. The samples were then neutralised and fatty acid methyl esters transferred into hexane for analysis by gas chromatography. Fatty acid methyl esters were separated on a BPX-70 fused silica capillary column (30 m x 0.2 mm x 0.25 μm, manufactured by SGE) in a HP6890 gas chromatograph fitted with a flame ionisation detector. Gas chromatography run conditions were as described elsewhere [15]. A Supelco® 37 Component FAME Mix was used as a calibration reference standard (Sigma-Aldrich, Irvine, UK). Fatty acid data for both total plasma and PC are expressed as % of total fatty acids present.

Measurement of plasma cytokine concentrations

The concentrations of TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12, and interferon (IFN)-γ were measured in plasma using a high sensitivity Bio-Techne multiplex immunoassay (R&D Systems, Abingdon, UK). Reagents were brought to room temperature before use and dilutions were prepared immediately before use according to the manufacturer's instructions. Samples were read using a Bio-Rad-plex Luminex Analyzer. Data are expressed as pg/ml plasma.

Statistical analysis

Data were checked for normality using the Kolmogorov-Smironov test. Much of the data were skewed and therefore all data are expressed as median and interquartile range. Comparisons were made between treatment groups at t_{END} using the Mann-Whitney U-test. Comparisons betwen t_{END} and t_{START} within a treatment group were made with the Wilcoxon signed rank test. Statistical analyses were performed using SPSS version 21. In all cases a value for $P < 0.05$ was taken to indicate a statistically significant difference.

Results

Patient characteristics

Data were only used when both the tSTART and tEND samples were available: tEND samples were not available for one patient in the SMOFLipid group and for 3 patients in the ClinOleic group. Thus, sample sizes in the two groups were 12 and 16, respectively. Table 1 shows the characteristics of these patients and of their nutrition support. Patients received about 20 g of lipid infused over 16 to 18 hours each day.

Effect of changing lipid emulsion on blood markers of liver function

Neither total bilirubin nor the three liver enzymes measured (ALT, AST, GGT) were altered by

transfer of patients from Intralipid to SMOFLipid for 60 days (Table 2). Total bilirubin was also not altered by transfer of patients from Intralipid to ClinOleic (Table 2). However, the concentration of GGT was significantly lower after 60 days of ClinOleic compared to before (P = 0.044; Table 2) and the concentrations of both ALT and AST tended to be lower after 60 days of ClinOleic (P = 0.093 and 0.066, respectively; Table 2). Figure 1 shows total bilirubin and each of the three liver enzymes at t_{START} and t_{END} for each individual patient according to their treatment group.

Effect of changing lipid emulsion on blood lipid concentrations

Plasma total cholesterol and triglyceride concentrations were not altered by either SMOFLipid or ClinOleic and were not different between the two groups after 60 days (Table 2).

Effect of changing lipid emulsion on plasma fatty acids

The fatty acid composition of total plasma lipid is shown in Table 3. Transfer of patients from Intralipid to SMOFLipid resulted in significant decreases in the proportions of linoleic acid, α-linolenic acid, 20:2n-6 (the elongation product of linoleic acid), di-homo-γ-linolenic acid (20:3n-6), and the EFA deficiency indicator mead acid (Table 3). In parallel, there were significant increases in the proportions of EPA, docosapentaenoic acid (22:5n-3) and DHA (Table 3). The ratio of mead acid to arachidonic acid was not significantly altered (t_{START}: 0.03 (0.02, 0.04) vs t_{END} 0.02 (0.02, 0.03); P = 0.191).

Transfer of patients from Intralipid to ClinOleic resulted in significant decreases in the proportions of palmitic acid (16:0), stearic acid (18:0), linoleic acid, 20:2n-6, di-homo-γ-linolenic acid (20:3n-6), arachidonic acid and mead acid, as well as all n-3 PUFAs including both EPA and DHA (Table 3). In parallel, there were significant increases in the proportions of palmitoleic acid (16:1n-7) and oleic acid (Table 3). The ratio of mead acid to arachidonic acid

was not significantly altered (t_{START}: 0.03 (0.02, 0.04) vs t_{END} 0.02 (0.02, 0.04); $P = 0.664$).

At the 60 day time point (t_{END}) the proportions of palmitic acid, stearic acid, dihomo-γ-linolenic acid, arachidonic acid, and all n-3 PUFAs including both EPA and DHA were higher in the SMOFLipid group than in the ClinOleic group (Table 3). Conversely, the proportions of oleic acid, α-linolenic acid and 20:1n-9 (the elongation product of oleic acid) were higher in the ClinOleic group than in the SMOFLipid group (Table 3). The ratio of mead acid to arachidonic acid was not different between the groups at 60 days ($P = 0.371$).

Generally similar data were observed in plasma PC (full data not shown). Here, transfer of patients from Intralipid to SMOFLipid significantly increased the proportions of both EPA (t_{START} 0.87 (0.68, 1.00) % vs t_{END} 1.71 (1.10, 2.19) %; $P = 0.015$) and DHA (t_{START} 1.35 (1.25, 1.52) % vs t_{END} 2.56 (1.95, 3.04) %; $P = 0.001$). In the SMOFLipid group there was no significant change in the ratio of mead acid to arachidonic acid in plasma PC (t_{START} 0.03 (0.02, 0.04) vs t_{END} 0.02 (0.02, 0.03); $P = 0.190$). In the ClinOleic group there was a significant decrease in the ratio of mead acid to arachidonic acid in plasma PC (t_{START} 0.07 (0.05, 0.10) vs t_{END} 0.04 (0.02, 0.04); $P = 0.001$).

No patient had a ratio of mead acid to arachidonic acid > 0.2 in either plasma total lipid or plasma PC; the highest ratios in plasma total lipid and in plasma PC were 0.05 and 0.19, respectively.

Effect of changing lipid emulsion on plasma cytokine concentrations

Concentrations of IL-1β, IL-12 and IFN-γ were below the limit of detection in most of the plasma samples. In contrast, IL-6, IL-8, IL-10 and TNF-α were easily detected in all samples and the concentrations of these four cytokines are reported in Table 4. The ratio of TNF-α to IL-10 is also reported (Table 4) as an ”inflammatory index” since TNF-α is pro-inflammatory and IL-10 is anti-inflammatory and the two act to oppose one another’s actions. The

concentrations of IL-6, IL-10 and TNF-α and the ratio of TNF-α to IL-10 were not altered by transfer to either SMOFLipid or ClinOleic (Table 4). The concentration of IL-8 decreased when the patients received ClinOleic for 60 days and at that time point the concentration was lower than in the SMOFLipid group (Table 4).

Discussion

HPN aims to prevent malnutrition in patients who cannot cover their nutritional requirements via the oral or enteral route for a prolonged period of time [1-3]. Lipid emulsions are essential components of PN formulations as a source of non-glucose calories and of fatty acids, including the EFAs linoleic acid and α-linolenic acid. Traditional lipid emulsions used in HPN are based on soybean oil and are rich in EFAs, especially linoleic acid. Newer lipid emulsions have been developed that have a lower content of linoleic acid, because there is a concern that soybean oil provides an excess of this fatty acid [4,11,16]. Concerns with excess soybean oil include liver disease and inflammation. This study compared the effect of transferring adults on long-term HPN from a soybean oil-based lipid emulsion to one of two new lipid emulsions for 8 weeks. The new lipid emulsions were ClinOleic, an 80:20 mix of olive oil and soybean oil, and SMOFLipid, a 30:30:25:15 mix of soybean oil, medium-chain triglyceride rich oil, olive oil and fish oil. ClinOleic is rich in oleic acid while SMOFLipid provides the bioactive long chain n-3 PUFAs EPA and DHA. Both ClinOleic and SMOFLipid might decrease liver disease and inflammation. However, because both these lipid emulsions are lower in EFAs than soybean oil, there is a concern that they might induce EFA deficiency. Therefore, the current study measured markers of liver function, inflammation, and fatty acid status including the marker of EFA deficiency. It was found that both lipid emulsions caused marked changes in fatty acid profile of plasma but that there was no evidence of EFA deficiency. However, despite the changes in fatty acids, SMOFLipid did not alter liver function markers, blood lipids or plasma

cytokines, while ClinOleic had only modest effects lowering one of four liver function markers (GGT) and one of three cytokines (IL-8).

The observed changes in fatty acid composition of plasma (and its PC component) are entirely consistent with the composition of the different lipid emulsions and provide clear evidence that use of either SMOFLipid or ClinOleic as a replacement for Intralipid in adult HPN will decrease the amount of linoleic acid in the blood. Furthermore, there is also a decrease in n-6 derivatives of linoleic acid. In parallel, ClinOleic increases oleic acid, while SMOFLipid increases EPA, docosapentaenoic acid and DHA. These effects of ClinOleic and SMOFLipid on fatty acid profiles are consistent with the limited literature in adult patients on HPN [17-20]. The observed effects of ClinOleic and SMOFLipid on oleic, linoleic, α-linolenic and arachidonic acids and on EPA and DHA are consistent with those reported in a variety of paediatric and adult patient groups as reviewed recently [21].

Interestingly, although the amount of EFAs provided in both ClinOleic and SMOFLipid is much less than in Intralipid (see Introduction), both resulted in a small decrease in the proportion of mead acid in plasma with no change in the ratio of mead to arachidonic acid ratio which was < 0.2 in all patients both prior to and at the end of the intervention. The latter observation suggests that neither SMOFLipid nor ClinOleic will induce EFA deficiency in adults on HPN. Again, this is consistent with the limited data on use of ClinOleic in adult HPN patients [17,18,20]. These findings indicate that the amount of linoleic and α-linolenic acids provided in both ClinOleic and SMOFLipid is sufficient to meet the requirement for EFAs in this patient group.

Prolonged use of Intralipid is considered to promote liver disease, which has been termed intestinal failure associated liver disease. This may be due to the high content of n-6 PUFAs or the presence of phytosterols [5]. Both ClinOleic and SMOFLipid contain a much lower amount

of n-6 PUFAs than Intralipid (see Introduction). SMOFLipid contains less phytosterols than Intralipid but the total amount is similar between Intralipid and ClinOleic, although the phytosterol composition is different [22]. SMOFLipid could offer advantages over Intralipid because EPA and DHA could modulate hepatic lipid metabolism and inflammation [4]. Fish oil containing lipid emulsions have been demonstrated to both prevent and reverse intestinal failure associated liver disease, particularly in paediatric patients [23], but also in adults [24]. In the current study SMOFLipid did not alter markers of liver function compared to when the patients were receiving Intralipid, while ClinOleic decreased GGT levels. Previous studies reveal little effect of ClinOleic on liver function markers in adult patients receiving HPN [17,18]; the lack of effect of ClinOleic on total bilirubin, AST and ALT in the current study is consistent with this. SMOFLipid was shown to lower bilirubin, ALT and AST in adults receiving HPN [19]. The latter study was of shorter duration than the current study (4 weeks vs 8 weeks) but was larger. However, the similarity of the tEND and tSTART data for liver function markers in the current study suggests that the lack of effect was not due to small sample size. Thus, it is not clear why SMOFLipid did not improve liver function markers in the current study. It may relate to the lack of an effect on inflammation (see below). Clearly more research is needed in this area to confirm whether lipid emulsions providing EPA and DHA can favourably benefit intestinal failure associated liver disease in adult patients receiving HPN.

The n-3 PUFAs EPA and DHA exhibit anti-inflammatory properties which have been most clearly demonstrated in model systems [8,9]. Oleic acid may also have some anti-inflammatory activity [25]. Using LEs containing EPA and DHA has been demonstrated to lower the blood concentrations of some inflammatory markers following surgery or in critical illness, as reviewed elsewhere [16]. The limited number of studies with ClinOleic in such hospitalised patients report no effect on inflammatory markers [16]. Studies in adult HPN patients report no effect of ClinOleic [17,18] or SMOFLipid [19] on blood markers of inflammation. Thus, the

lack of effect of SMOFLipid on inflammation and the limited effect of ClinOleic seen in the current study is consistent with the small amount of literature that exists in this patient group. It may be that these patients are insufficiently inflamed for n-3 PUFAs, or oleic acid, to exert an anti-inflammatory effect.

One limitation of the current study is that patients were not randomly allocated to the lipid. they received. In addition, only a single time point was assessed (8 weeks). It might be important to investigate the time course of changes to an altered lipid regimen. In this context, an earlier study [19] reported that after 4 weeks, SMOFLipid lowered bilirubin, ALT and AST in adults receiving HPN.

Conclusions

Both SMOFLipid and ClinOleic significantly alter the fatty acid profile of plasma in adult HPN patients previously using Intralipid. Neither lipid emulsion induces EFA deficiency in these patients. SMOFLipid did not alter liver function markers or inflammation. In contrast, ClinOleic decreased some, though not all, markers of liver function and inflammation. SMOFLipid and ClinOleic may both be considered for use in adult HPN patients.

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Roles of the authors

SO designed the study and was responsible for its overall conduct. MK, JS, MO and MR identified patients for inclusion in the study. SO, MK and JS carried out the intervention. JT

and KM were responsible for supervising the procedure of changing the lipid emulsions and drew the blood samples. HLF determined fatty acid and cytokine concentrations under the supervision of PCC. HLF and PCC performed the statistical analysis. PCC drafted the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

SO, MK, JS, JT, KM, MO, MR and HLF have no conflict of interest to declare. PCC acts as an advisor to Fresenius-Kabi, B. Braun Melsungen and Baxter Healthcare.

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Figure caption

Figure 1. Individual data for total bilirubin and three liver enzymes at t_{START} and t_{END} according to treatment group.

415 Table 1. Characteristics of the patients who completed the study.
416

Parameter	SMOFLipid	Clinoleic
Number of patients	12	16
Age (years)*	57.4 (34-69)	63.8 (29-79)
Sex		
Male	7	6
Female	5	10
Etiology of intestinal failure		
Ischemia	4	4
Leśniowski-Crohn disease	3	4
Obstruction	1	2
Mucosal disfunction	1	3
Surgery complication	3	3
Duration of home TPN (years)*	3.8 (2 -11)	5.1 (2-12)
Macronutrient intake from TPN (g/infusion)*		
Amino acids	50 (49-60)	49 (45-62)
Glucose	205 (165-265)	225 (170-280)
Lipid	20 (20-20)	22 (20-30)
Energy from TPN (kcal/infusion)*	1180 (1000-1450)	1210 (1050-1420)

417 *Data are mean (range)

Table 2. Blood markers of liver function and blood lipids in the two treatment groups before (t_{START}) and after (t_{END}) 60 days of a new lipid emulsion as part of HPN.

	SMOFLipid (n = 12)				ClinOleic (n = 16)				
	Normal range	t_{START}	t_{END}	*P**	Normal range	t_{START}	t_{END}	*P**	$P^{‡}$
Total bilirubin (mg/dL)	0-1.2	0.50 (0.40, 1.00)	0.50 (0.40, 1.20)	0.204	0.2-1.3	0.50 (0.40, 0.80)	0.55 (0.40, 0.85)	0.573	0.960
ALT (U/L)	0-33	47.0 (31.0, 76.0)	47.0 (29.0, 105.0)	1.000	14-59	29.5 (20.0, 51.0)	24.5 (20.5, 32.5)	0.093	0.028
AST (U/L)	0-33	27.0 (20.0, 37.0)	25.0 (20.0, 49.0)	0.755	14-36	31.5 (23.0, 48.5)	25.5 (22.5, 35.5)	0.066	0.265
GGT (U/L)	6-42	43.0 (16.0, 158.0)	42.0 (27.0, 108.0)	0.575	12-43	69.0 (46.5, 141.0)	49.0 (27.5, 109.0)	0.044	0.657
Total cholesterol (mg/dL)	< 190	127.0 (112.0, 174.0)	131.0 (110.0, 163.0)	0.705	< 190	163.0 (139.0, 176.5)	155.5 (142.0, 182.0)	0.746	0.073
Triglycerides (mg/dL)	< 150	122.0 (85.0, 127.0)	100.0 (95.0, 134.0)	0.508	< 150	94.5 (78.5, 121.0)	83.5 (72.0, 161.0)	0.756	0.267

Data are median (25th percentile, 75th percentile)

**P* value for comparison t_{END} vs t_{START} within a treament group (Wilcoxon signed ranks test)

‡*P* value for comparison between treatment groups at t_{END} (Mann Whitney U-test)

Table 3. Fatty acid composition of total plasma lipid (each fatty acid as a% of total fatty acids present) in the two treatment groups before (t_{START}) and after (t_{END}) 60 days of a new lipid emulsion as part of HPN.

		SMOFLipid (n = 12)			ClinOleic (n = 16)			
Fatty acid	Common name	t_{START}	t_{END}	*P**	t_{START}	t_{END}	*P**	$P^{\ddagger}$
14:0	Myristic	0.39 (0.32, 0.41)	0.33 (0.25, 0.45)	0.460	0.39 (0.28, 0.57)	0.71 (0.54, 0.88)	0.004	< 0.001
16:0	Palmitic	30.0 (29.3, 30.6)	30.7 (29.1, 31.7)	0.409	29.9 (28.8, 31.0)	24.6 (22.9, 27.7)	< 0.001	< 0.001
16:1n-7	Palmitoleic	0.69 (0.56, 1.18)	0.89 (0.60, 1.20)	0.071	1.25 (1.06, 1.55)	3.64 (2.47, 4.30)	< 0.001	< 0.001
18:0	Stearic	14.3 (13.9, 14.8)	14.1 (13.0, 15.2)	0.555	14.2 (13.6, 15.7)	8.7 (7.9, 9.7)	0.001	< 0.001
18:1n-9	Oleic	11.4 (10.8, 13.9)	11.9 (10.9, 13.3)	0.657	12.9 (11.7, 14.7)	19.9 (18.6, 25.9)	< 0.001	< 0.001
18:1n-7	Vaccenic	2.3 (2.2, 2.6)	2.4 (2.1, 2.8)	0.467	2.8 (2.3, 3.4)	2.9 (2.6, 3.2)	0.748	0.107
18:2n-6	Linoleic	18.3 (15.8, 20.3)	15.4 (14.9, 18.7)	0.042	20.4 (18.7, 21.0)	14.0 (11.9, 16.5)	0.001	0.057
18:3n-3	α-Linolenic	0.31 (0.25, 0.37)	0.23 (0.19, 0.27)	0.030	0.36 (0.23, 0.59)	0.50 (0.42, 0.57)	0.203	< 0.001
20:1n-9	Gondoic	0.13 (0.12, 0.17)	0.14 (0.13, 0.18)	0.341	0.18 (0.14, 0.26)	0.20 (0.15, 0.25)	0.975	0.018
20:2n-6	Eicosadecaanoic	0.37 (0.33, 0.46)	0.26 (0.22, 0.29)	0.019	0.50 (0.34, 0.77)	0.35 (0.26, 0.41)	0.018	0.095
20:3n-9	Mead	0.28 (0.21, 0.37)	0.20 (0.13, 0.25)	0.030	0.34 (0.21, 0.52)	0.21 (0.12, 0.30)	0.031	0.537
20:3n-6	Dihomo-γ-linolenic	4.0 (3.4, 4.8)	3.3 (2.9, 3.7)	0.001	3.7 (3.2, 4.1)	1.8 (1.6, 2.3)	< 0.001	< 0.001
20:4n-6	Arachidonic	9.8 (9.1, 10.4)	8.8 (7.6, 10.4)	0.192	11.8 (9.14, 13.56)	7.5 (6.5, 10.5)	0.008	0.041
20:3n-3	Eicosatriaenoic	0.12 (0.11, 0.14)	0.12 (0.09, 0.13)	0.128	0.14 (0.13, 0.15)	0.09 (0.07, 0.11)	0.001	0.254
20:4n-3	Eicosatetraenoic	0.34 (0.33, 0.41)	0.38 (0.35, 0.43)	0.082	0.27 (0.25, 0.31)	0.15 (0.12, 0.19)	0.001	< 0.001
20:5n-3	Eicosapentaenoic (EPA)	1.09 (0.79, 1.36)	2.19 (1.70, 2.47)	0.008	0.93 (0.80, 1.57)	0.59 (0.46, 1.20)	0.044	< 0.001
24:0	Lignoseric	0.41 (0.37, 0.46)	0.29 (0.27, 0.33)	< 0.001	0.45 (0.40, 0.50)	0.30 (0.26, 0.39)	0.003	0.415
22:5n-3	Docosapentaenoic	1.14 (0.92, 1.36)	1.42 (1.16, 1.59)	0.002	1.01 (0.91, 1.28)	0.62 (0.44, 0.74)	0.001	< 0.001
22:6n-3	Docosahexaenoic (DHA)	2.45 (2.06, 2.85)	4.70 (3.91, 4.85)	< 0.001	3.14 (2.78, 4.18)	1.55 (1.36, 2.02)	0.001	< 0.001

Data are median (25th percentile, 75th percentile)

*P value for comparison t_{END} vs t_{START} within a treament group (Wilcoxon signed ranks test)

ǂP value for comparison between treatment groups at t_{END} (Mann Whitney U-test).

Table 4. Plasma concentrations of cytokines (pg/ml) in the two treatment groups before (t_{START}) and after (tEND) 60 days of a new lipid emulsion as part of HPN.

	SMOFLipid (n = 12)			ClinOleic (n = 16)			
	t_{START}	t_{END}	*P**	t_{START}	t_{END}	*P**	$P^{‡}$
IL-6	14.0 (11.0, 22.0)	17.0 (10.0, 20.0)	0.502	22.25 (10.75, 62.50)	17.0 (9.5, 33.5)	0.289	0.587
IL-8	856.5 (392.0, 1438.5)	646.8 (446.5, 978.0)	0.530	611.25 (464.25, 839.00)	526.2 (416.2, 645.0)	0.030	< 0.001
IL-10	19.5 (14.2, 22.2)	17.7 (15.5, 21.0)	0.387	17.50 (13.75, 33.50)	23.0 (14.7, 31.0)	0.756	0.377
TNF-α	43.5 (36.5, 61.0)	47.5 (35.2, 53.5)	0.814	51.75 (36.25, 70.50)	44.0 (34.2, 58.2)	0.108	< 0.001
TNF-α/IL-10	2.44 (2.10, 3.06)	2.43 (2.03, 2.95)	0.646	2.25 (1.34, 3.47)	1.95 (1.51, 2.65)	0.252	0.320

Data are median (25th percentile, 75th percentile)

**P* value for comparison t_{END} vs t_{START} within a treament group (Wilcoxon signed ranks test)

‡*P* value for comparison between treatment groups at t_{END} (Mann Whitney U-test)