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ORIGINAL CONTRIBUTION

# Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients

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**Summary** *Objective* We assessed the effects of a novel lipid emulsion with reduced content of n-6 fatty acids (FA), increased share of MUFA and n-3 FA and supplemental vitamin E on fatty acid and leukotriene pattern in surgical patients. *Methods* In a double-blind, randomized study 33 patients received isonitrogenous, isocaloric TPN over 5 postoperative days following major abdominal surgery. 19 patients received the new SMOFlipid® 20 % and 14 patients a standard soybean oil emulsion (Lipovenoes® 20 %, both Fresenius Kabi), each 1.5 g fat/kg body weight (BW)/d. Routine lipid biochemistry, plasma tocopherol, fatty acid pattern in plasma phospholipids, as well as leukotriene (LT) release in leukocytes were assessed. Additionally, fatty acid pattern in leukocyte and platelet phospholipids were analysed, but results are not presented. *Results* On day 6, plasma α-tocopherol (34.2 ± 10.3 vs. 17.6 ± 2.9 μmol/L) and, in plasma PL, total n-3 FA were higher (11.1 ± 1.9 vs. 4.9 ± 0.9 mol%; $p < 0.05$) and total n-6 FA lower (23.8 ± 2.2 vs. 31.8 ± 1.7 mol%; $P < 0.05$); the ratio n-3/n-6 FA being elevated (0.5 ± 0.1 vs. 0.2 ± 0.0 $p < 0.05$) with SMOFlipid compared to the soybean oil emulsion. The shares of EPA (3.3 ± 1.0 vs. 0.4 ± 0.2 mol%; $p < 0.05$) and DHA (6.9 ± 1.8 vs. 3.7 ± 0.8 mol%; $p < 0.05$) were highly increased but that of arachidonic acid (AA) was unchanged with SMOFlipid while the ratio EPA/AA was increased (0.7 ± 0.2 vs. 0.1 ± 0.0 $p < 0.05$). $LTB_5$ release was enhanced on day 6 (8.1 ± 5.3 vs. 1.8 ± 3.8 pmol/$10^7$ PMN, $p < 0.05$) and liberation of $LTB_4$ was lowered, yet not significantly with SMOFlipid (124.0 ± 51.2 vs. 152.1 ± 68.8 pmol/$10^7$ PMN). Length of hospital stay was significantly shorter with SMOFlipid (13.4 ± 2.0 vs. 20.4 ± 10.0 days, $p < 0.05$). *Conclusion* Treatment with the new emulsion SMOFlipid is well tolerated and modulates FA and leukotriene pattern suggesting favourable anti-inflammatory effects and further clinical benefits.

**Key words** lipid emulsion – TPN – fish oil – olive oil – vitamin E – immunomodulation

## Introduction

In clinical nutrition, lipids are more than sources of energy and building blocks for cell membranes. They may also be considered as pharmacological agents provided by nutrition, thus emphasising the major role of the quality of lipid intake in the clinical context [1, 2]. Excessive intake of polyunsaturated fatty acids (PUFA), especially linoleic acid, impairs synthesis of long-chain

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PUFA by inhibiting their desaturation pathways [3, 4], resulting in imbalanced synthesis of eicosanoids. In addition, suppressive effects of PUFAs on immune cell function have been reported [4–6]. Indeed, increased susceptibility to infection is to be seriously considered as a disadvantage especially in patients at risk of sepsis and SIRS. There is, however, a substantial uncertainty about the mechanisms whereby lipids modulate inflammation; certainly lipids modulate the composition of plasma membranes both in cells producing pro-inflammatory cytokines and in those which are targets of their action [7].

Recently, a NIH working group recommended that the amount of dietary n-6 fatty acids (FA) should be reduced and the share of n-3 FA increased [8]. These measures were considered as mandatory for optimal brain and cardiovascular health and function. Furthermore, it was recommended that the majority of FA should be obtained from monounsaturated fatty acids (MUFA) [8]. The question might be raised whether this public health related recommendation can be implicated in clinical nutrition.

In the present study we investigated the effects of a newly developed lipid emulsion made of a physical mixture of soybean oil (long-chain), medium-chain, olive oil and fish oil triglycerides (SMOFlipid 20%). The new emulsion contains an increased amount of vitamin E (approx. 200 mg per litre) in order to counteract peroxidation but also to avoid immunosuppression due to decreased antioxidant capacity [9].

We hypothesised that the novel emulsion with reduced content of n-6 FA, increased amount of n-3 FA and MUFA, might exert beneficial antiinflammatory and immunomodulatory effects.

## Material and methods

### Patients and nutrition

In a randomised, double blind study 33 patients derived from two centres [University hospitals Münster (n = 12, centre 1) and Gießen (n = 21, centre 2), respectively] received isonitrogenous (1.5 g amino acids/kg body weight (BW) isoenergetic (33 kcal/kg BW) total parenteral nutrition over 5 postoperative days following major abdominal surgery. Patient characteristics are given in Table 1. All patients were apparently well nourished. Patients with manifest metabolic diseases (e. g. diabetes mellitus, hyperlipidaemia), overweight (body mass index > 30 kg/m$^2$), chronic renal, liver or heart diseases, acute or life-threatening diseases, history of drug abuse or chronic alcoholism, or concomitant corticosteroid therapy were excluded. The study was approved by the local Ethical Committees according to German law and the procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1996. Written informed consent of each patient was obtained before commencement of the investigation.

**Table 1** Patient characteristics

| | Lipovenoes 20% | SMOFlipid 20% |
|---|---|---|
| Number of patients (n) | 14 | 19 |
| Male/female | 12/2 | 12/7 |
| Mean age (years ± SD) | 61.1 ± 10.5 | 63.1 ± 14.2 |
| Mean weight (kg ± SD) | 77.7 ± 11.9 | 72.9 ± 11.3 |
| Mean height (cm ± SD) | 176.9 ± 7.7 | 168.9 ± 9.4 |
| Duration of surgery (hours ± SD) | 3.58 ± 1.40 | 3.47 ± 1.25 |

*SD* standard deviation

The novel emulsion (SMOFlipid® 20%, Fresenius Kabi, Bad Homburg, Germany) is a physical mixture of soybean oil (60 g/L), MCT (60 g/L), olive oil (50 g/L) and fish oil (30 g/L). The emulsion was supplemented with vitamin E which is important for antioxidant protection, and contained about 200 mg/L vitamin E. Nineteen patients received the new emulsion, and 14 patients a standard soybean long-chain triglyceride emulsion (Lipovenoes® 20%, Fresenius Kabi, Bad Homburg, Germany), which contains 200 g soybean oil/L and 57 mg vitamin E/L [10]. Each fat regimen corresponded to 1.5 g lipids/kg BW/day. The fatty acid composition of SMOFlipid and Lipovenoes are given in Table 2.

During the study, all patients were monitored daily for vital signs (arterial blood pressure, heart rate, body temperature and body weight) and complicating factors like allergic reactions, nausea, dysfunction of the gastrointestinal tract, signs of infection, cardiac discomforts, pulmonary affections, renal or hepatic dysfunction, haematological signs or behavioural disorders. Concomitant medications, fluid input and blood substitution were carefully monitored. For clinical outcome assessment, length of postoperative hospital stay was monitored.

Heparin blood was drawn before and the day after operation and on the subsequent days of infusion in order to monitor lipid metabolism (serum triglycerides, total cholesterol, phospholipids), before start of infusion and on the 6$^{th}$ postoperative day to screen FA profiles and vitamin E concentrations, and before infusion and on the 4$^{th}$ and 6$^{th}$ postoperative days to measure stimulus-induced eicosanoid release by leukocytes.

### Analytical methods

Serum triglycerides, total cholesterol, and phospholipids were assayed using commercially available kits (Boehringer, Mannheim, D) using a Hitachi 717 autoanalyser.

**Table 2** Fatty acid pattern of lipid emulsions [mean value in g/L]

| | Lipovenoes 20% | SMOFlipid 20% |
|---|---|---|
| C6:0 | | 0.2 |
| C8:0 | | 32.0 |
| C10:0 | | 23.4 |
| C12:0 | | 0.4 |
| C14:0 | 0.2 | 1.8 |
| C16:0 | 23.1 | 18.2 |
| C16:1 | 0.3 | 3.4 |
| C18:0 | 8.7 | 5.5 |
| C18:1n-9 | 44.8 | 56.2 |
| C18:2n-6 | 102.1 | 37.8 |
| C18:3n-3 | 15.9 | 5.4 |
| C18:4n-3 | | 0.9 |
| C20:0 | 0.8 | 0.5 |
| C20:1 | 0.5 | 0.7 |
| C20:4n-6 | 0.4 | 1.0 |
| C20:5n-3 | | 4.7 |
| C22:0 | 1.0 | 0.4 |
| C22:1 | | 0.3 |
| C22:5n-3 | | 0.7 |
| C22:6n-3 | | 5.3 |
| Others | | 3.4 |
| n-3/n-6 | 1/6.4 | 1/2.3 |

**FAs in plasma, leukocyte and platelet phospholipids.** Lipids were extracted with chloroform: methanol (1:1 vol./vol.) containing 50 mg/L butylhydroxytoluol (BHT). Margaric acid 0.1 mg was added to the samples as an internal standard. The chloroform phase was dried under a nitrogen stream and resuspended in 2 mL methanol: hexane (4:1 vol/vol, containing 50 mg/L BHT). Acetylchloride (0.2 mL) was added to the samples drop by drop. After 60 min incubation in a shaking water bath at 100 °C, samples were cooled and dissolved with 5 mL 6 % $K_2CO_3$. After centrifugation (2600 × g, 10 min., 4 °C), the hexane containing upper phase could be analysed by gas chromatography as previously described [11].

**Neutrophil leukotriene profile.** PMNs were isolated according to the method of Hjorth et al. [12]. Cell viability, as assessed by trypan blue exclusion, ranged above 96 % under all experimental conditions, and LDH release was consistently below 3 %. PMNs were stimulated for 10 min. with 1 µmol/L A23187 and leukotrienes of the 4- and 5-series were extracted by solid phase extraction as previously described [13]. RP-HPLC was carried out on octadecylsilyl columns (Hypersil 5-µm-particles) with a mobile phase of methanol/water/acetic acid (72:28:0.16, pH 4.9) and followed by UV detection at 270 nm and photodiode array detection (Waters 990), respectively, to quantify leukotrienes and control peak purity. For additional verification, samples were collected in 15-s fractions in selected experiments and subjected to post HPLC-RIA with anti-$LTB_4$, as previously described [13].

**Vitamin E.** Plasma concentration of α-tocopherol was analysed by HPLC as described previously [14].

## Statistical analysis

Statistical analysis was performed using the "two one-sided test" procedure of Dunnett and Gent and ANOVA. Significance level was p less than 0.05. Data are presented as mean ± SD.

## Results

The two treatment groups were similar with respect to demographic characteristics. In both groups, the most frequent types of main surgical intervention were operation on oesophagus, as well as gastric and intestinal operations, followed by rectal and perirectal operations and biliary tract operation. The new lipid emulsion was well tolerated and no undesirable clinical effects were recorded. Routine lipid biochemistry (difference at day 6 to pre-infusion values of triglycerides, phospholipids and total cholesterol) was similar in both groups (results not shown).

Initial concentrations of phospholipid derived linoleic acid, α-linolenic acid, arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), the total n-3 und n-6 fatty acids (n-3 FA and n-6 FA) in plasma as well as their ratio were similar in both groups (Table 3). Compared with the initial values, the contents of phospholipid derived total n-3 FA, EPA and DHA were higher and linoleic acid, AA and total n-6 FA were lower after 6 days; the ratios n-3/n-6 FA and that of EPA and AA were profoundly elevated with the new SMOFlipid emulsion (Table 3). Phospholipid derived FA patterns in leukocytes and platelets were similar to those seen in plasma phospholipids (results not shown).

Initial concentrations of leukotriene $B_4$ and leukotriene $B_5$ ($LTB_4$ and $LTB_5$) were similar in both groups. $LTB_5$ release was enhanced on day 6 whereas the liberation of $LTB_4$ was lowered with SMOFlipid, consequently the ratio of $LTB_5/LTB_4$ was increased (Table 4). The ratio of $LTB_5/LTB_4$ in the control group remained unchanged.

Initial values of plasma α-tocopherol were similar in both groups (SMOFlipid: 14.46 ± 6.51 µmol/L vs. standard lipid emulsion: 11.56 ± 2.26 µmol/L). On day 6, plasma α-tocopherol was significantly higher with

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**Table 3** Phospholipid derived fatty acid patterns in plasma (mol%) before infusion and on the 6th postoperative day, values are given as mean ± SD

| | Lipovenoes 20% | | SMOFlipid 20 % | |
|---|---|---|---|---|
| | Before inf. | 6th day | Before inf. | 6th day |
| Total n3-FA | 6.53 ± 1.37 | 4.93 ± 0.89 | 6.76 ± 1.63 | 11.09 ± 1.93* |
| Total n6-FA | 30.51 ± 1.97 | 31.77 ± 1.75 | 29.46 ± 3.34 | 23.76 ± 2.19* |
| Ratio n3/n6 | 0.22 ± 0.06 | 0.16 ± 0.03 | 0.23 ± 0.07 | 0.47 ± 0.09* |
| Linoleic acid | 20.49 ± 2.95 | 24.26 ± 2.56 | 19.93 ± 3.21 | 15.92 ± 2.03* |
| α-Linolenic acid | 0.20 ± 0.09 | 0.27 ± 0.07 | 0.18 ± 0.04 | 0.22 ± 0.07 |
| AA | 6.56 ± 2.08 | 4.31 ± 1.09 | 6.51 ± 1.00 | 5.02 ± 0.58* |
| EPA | 0.63 ± 0.41 | 0.44 ± 0.18 | 0.64 ± 0.33 | 3.32 ± 0.97* |
| DHA | 4.95 ± 0.94 | 3.75 ± 0.80 | 5.05 ± 1.46 | 6.88 ± 1.81* |
| Ratio EPA/AA | 0.10 ± 0.07 | 0.10 ± 0.03 | 0.10 ± 0.05 | 0.66 ± 0.17* |

* indicates a statistically significant difference between test groups

**Table 4** Leukotriene release (pmol/$10^7$ PMN) before infusion and on the 6th postoperative day, values are given as mean ± SD

| | Lipovenoes 20% | | SMOFlipid 20% | |
|---|---|---|---|---|
| | Before inf. | 6th day | Before inf. | 6th day |
| $LTB_4$ | 147.17 ± 78.84 | 152.10 ± 68.79 | 142.78 ± 88.37 | 124.01 ± 51.18 |
| $LTB_5$ | 1.00 ± 2.12 | 1.83 ± 3.76 | 3.31 ± 3.40 | 8.14 ± 5.30 * |
| $LTB_5/LTB_4$ | 0.01 ± 0.03 | 0.01 ± 0.02 | 0.03 ± 0.03 | 0.07 ± 0.05 * |

* indicates a statistically significant difference between test groups

SMOFlipid compared to the control group (34.2 ± 10.3 vs. 17.6 ± 2.9 μmol/L, $p < 0.05$).

A reduced length of hospital stay with SMOFlipid compared to soybean oil was observed in this study (13.4 ± 2.0 vs. 20.4 ± 10.0 days, $p < 0.05$).

## Discussion

Nearly 2 million years ago our prehistoric, Palaeolithic ancestors probably consumed an equal mix of n-3 and n-6 FA [15] like the Inuit or Alaskan diet [16, 17]. The considerable dietary excess of n-6 FA decreased temporarily the n-3/n-6 ratio to yield 1:16.8 [8, 18] and is now 1:7–8 [19]. It is interesting to note that the intake of PUFA rose from 4% of dietary energy in the early 1970s to 6% at present. The direct consequence might be the upsurge of asthma [20], unexplained increase in the incidence of eczema and allergic rhinitis as well as inflammatory diseases [7, 20–22].

Major questions include which n-3/n-6 FA ratio is the most advantageous in the clinical context and whether provision of a lipid emulsion with an optimum ratio would be associated with metabolic and clinical benefits [23]. Based on previous investigations and according to current knowledge a n-3 to n-6 FA ratio between 1:4 and 1:2 can be considered as beneficial for the severely ill patient [23–27]. There is some evidence that a n-3 to n-6 FA ratio of about 1:3–1:2 induces the highest leukotriene $C_5/C_4$ ratios and thus exerts the most favourable modulation of synthesis of the anti-inflammatory lipid mediators [23–26]. In the newly developed lipid emulsion (SMOFlipid) the n-3/n-6 FA ratio was adjusted to yield the proposed optimum ratio.

The reduced content of n-6 FA in the new emulsion might have several beneficial effects related to immune defence and inflammatory reactions [1]. Recent advances indicate great potential for fish oil containing emulsions. The possible mechanisms involve suppression of excessive endothelial activity and thereby decreased production of pro-inflammatory mediators. This implicates that fish-oil nutrition with n-3 FA may reduce inflammatory and thrombotic responses while protecting tissue microperfusion and immunity [7, 27]. Consequently, supplemental n-3 FA might be a valuable tool to improve standard clinical therapy, especially in chronic hyperinflammatory diseases and as an adjunct therapeutic measure after trauma, injury and during episodes of early sepsis [28]. Suppression of T-cell mediated immune function is a possible adverse effect associated with the administration of excessive amounts of fish oil [9, 29, 30]. With the new emulsion only moderate amounts of n-3 FA, corresponding to 15% fish oil of total lipids, were given. Another reason for immunosuppression might be due to lipid peroxidation and decreased antioxidant capacity. In order to prevent these problems, the new lipid emulsion was substituted with vitamin E, the main lipophilic antioxidant. Supplemen-

tation of a n-3 FA containing emulsion with vitamin E was shown to reduce free radicals and lipid peroxidation [31]; therefore it is conceivable that the total content of approx. 200 mg vitamin E/L in SMOFlipid counteracted free radical generation and, thus, served as an appropriate antioxidant source. In the present study, the plasma α-tocopherol concentration was significantly higher in the SMOFlipid group than in the control group on the sixth postoperative day. This is in accordance with a clinical study in twenty intensive care unit patients receiving SMOFlipid or a standard soybean oil emulsion [32]. The study results showed that the α-tocopherol concentration in plasma significantly increased in SMOFlipid-treated patients, reaching healthy control subject mean values. Furthermore, there was only a slight decrease of plasma antioxidant capacity with SMOFlipid despite its high n-3 FA content, and the antioxidant capacity was similar in the SMOFlipid group and the standard soybean oil group.

The fatty acid compositions of plasma phospholipids was markedly affected by the compositions of the lipid emulsions. Infusion of standard soybean oil emulsion led to an enrichment of linoleic acid, whereas the concentrations of long-chain n-3 FA were significantly increased with SMOFlipid infusion. The considerable increases of EPA and DHA in leukocyte membrane phospholipids as well as the profound increase of leukotriene $B_5$ as well as the decrease in leukotriene $B_4$ synthesising capacity indicate high metabolic activity at the site of the 5-lipoxygenase and thus suggest immunomodulation. Our results are in good agreement with those in active Crohn's disease [33] and following major operations [11, 34].

The anti-inflammatory pattern observed with the new emulsion is expected to be associated with beneficial features of the immune system and further clinical benefits. Accordingly, in the present study a significantly shorter length of hospital stay was observed in SMOFlipid treated patients compared with the standard lipid emulsion, which is in line with previous findings. A reduction of length of hospital stay has been demonstrated for postoperative as well as perioperative parenteral nutrition with an intravenous fish oil supplement (Omegaven®, Fresenius Kabi) in surgical patients [35, 36].

The MCT components might bear the advantages of efficient hydrolysis by lipoprotein lipase and the rapid plasma elimination of derived small sized remnants [1]. The portion of MCT might be preferentially oxidised sparing essential FA for incorporation into cell membranes [37].

The new lipid emulsion contains 25 % olive oil, mainly oleic acid and thus contributes to decreasing the share of n-6 FA in the new preparation. Indeed, olive oil offers an immunologically neutral alternative for the use in TPN since olive oil does not affect membrane composition and therefore has little effect on eicosanoid production and immune response [1, 38].

The overall results indicate beneficial effects on postoperative immune response in surgical patients, with a new generation of lipid emulsions containing a physical mixture of soybean, MCT, olive and fish oil.

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