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Impact of *n*-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery

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In various diseases *n*-3 fatty acids exert anti-inflammatory properties. These effects seem to be related to the uptake and incorporation of eicosapentaenoic acid (EPA) into the cellular substrate pool after dietary intake of EPA, which is contained in fish oils (FO). In the state of inflammation EPA is released to compete with arachidonic acid (AA) for metabolism at the cyclo-oxygenase and the 5-lipoxygenase level. The metabolites of EPA have less inflammatory and chemotactic potency than the substances derived from AA. In addition to positive effects, early studies pointed towards prolonged bleeding times after dietary intake of *n*-3 fatty acids. This study was undertaken to address the issue of potential coagulation disturbances associated with postoperative parenteral FO administration. This was a prospective, randomised, double blinded clinical trial, carried out in two operative intensive care units (13 and 16 beds) in a university hospital. Forty-four patients undergoing elective major abdominal surgery participated in the trial. Patients were randomly assigned to receive total parenteral nutrition (TPN) supplemented with either soybean oil (SO, Lipovenoes® 10 % PLR; 1.0 g/kgBW per day; *n* = 20) for five days or with a combination of FO and SO (FO, Omegaven®; 0.2 g/kgBW per day plus SO, Lipovenoes® 10 % PLR; 0.8 g/kgBW per day, *n* = 24), respectively. Blood samples were taken preoperatively (day -1), prior to (day 1) during (days 2–5) and after TPN (day 6). The coagulation parameters thromboplastin time (Quick), activated partial thromboplastin time (aPTT), fibrinogen and antithrombin III were measured. To differentially assess activation levels of extrinsic and intrinsic coagulation pathway, factors VIIa and XIIa were quantified. Moreover platelet function was determined by resonance thrombography. Baseline values of coagulation and platelet function were comparable in both groups, but coagulation activity dropped after surgery. Over the observation period of 6 days, however, physiological levels were regained. No clinically significant differences were observed between the SO- and SO + FO- group. These findings suggest that infusion of fish oil in doses up to 0.2 g/kgBW per day is safe regarding coagulation and platelet function.

n-3 Fatty acids: Fish oil: Haemostasis: Coagulation

Introduction

After the epidemiological studies of Dyerberg & Bang, in which it has been shown, that Eskimos have a lower incidence of thrombosis, coronary heart disease and myocardial infarction, interest was focused on *n*-3 polyunsaturated fatty acids (*n*-3 PUFA) (Dyerberg *et al.* 1975, 1978, 1979). Compared with the European control group, the content of *n*-3 PUFA (contained in fish-oil,

FO), especially of *cis* 5,8,11,14,17-eicosapentaenoic acid (EPA) was increased in thrombocytes of Eskimos. Since then, numerous studies *in vitro*, as well as *in vivo* have been carried out, which showed anti-inflammatory properties of *n*-3 PUFA (Leaf, 1990) in various diseases, such as coronary heart disease (Burr *et al.* 1989), burns (Alexander & Gottschlich, 1990) severe multiple trauma (Bastian *et al.* 1998) and acute respiratory distress (ARDS; Gadeck *et al.* 1999).

Abbreviations: EPA, eicosapentaenoic acid; FO, fish oil; AA, arachidonic acid; TPN, total parenteral nutrition; SO, soybean oil; aPTT, activated partial thromboplastin time; PUFA, polyunsaturated fatty acid; AT, antithrombin; RTG, resonance thrombography.

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Table 1. Demographic characteristics, mean (SD)

Patients	SO (<i>n</i> = 20)	SO + FO (<i>n</i> = 24)	<i>P</i>
Age (y)	60.8 (10.9)	61.0 (12.6)	0.96
Gender (male/female)	14/6	18/6	1.00
SAPS II at entry ^a	12.0 (5.2)	12.4 (5.2)	0.80
Body mass index	24.5 (4.1)	25.2 (4.4)	0.56
Surgery (min)	346 (77)	349 (76)	0.91
Surgical procedure			0.74
Esophagectomy	3	4	
Gastrectomy	8	10	
Whipple procedure	8	10	
Total colectomy	1	0	

^aSimplified Acute Physiology Score II (Le Gall *et al.* 1993).

n-3 PUFA are capable of preventing hyperinflammatory processes by cell to cell signal modulation (Grimm *et al.* 1995). On one hand, the reduced release of pro-inflammatory arachidonic acid metabolites and platelet activating factor, and on the other hand, increased formation of anti-inflammatory *n*-3 eicosanoids might account for a *n*-3 PUFA dependent decrease of tumour necrosis factor α (Endres *et al.* 1989) and interleukin (IL) -1 (Molvig *et al.* 1991) production by monocytes. In previous studies we demonstrated a decreased inflammatory pulmonary vascular response due to FO-infusion. Blunted lung oedema formation was observed due to reduced pulmonary vascular resistance and permeability (Koch *et al.* 1993, 1995; Breil *et al.* 1996). After studies demonstrating improved survival following cecal ligation and puncture in FO supplemented rats (Johnson *et al.* 1993) neutrophils from septic patients stimulated *ex vivo* generated an altered lipid mediator spectrum reflecting the *n*-3 content of the administered fatty acid emulsions. Moreover pro-inflammatory cytokine levels were decreased (Grimminger, 1995). Beneficial effects of FO on pulmonary vasculature as postulated by our group (Koch *et al.* 1993, 1995; Breil *et al.* 1996) were confirmed in a recent publication (Gadeck *et al.* 1999) in 146 patients with ARDS. Due to improvement of pulmonary gas exchange as indicated by augmentation of the P_aO_2/F_iO_2 ratio, lower levels of F_iO_2 - and positive endexpiratory

pressure (PEEP) were required for an adequate oxygenation. Accordingly the number of respirator free days was increased under *n*-3 PUFA supplementation and intensive care unit (ICU)- stay was shortened (Gadeck *et al.* 1999).

Compared with European controls, decreased levels of myocardial infarction in Greenland Eskimos, as observed in early epidemiological studies (Dyerberg *et al.* 1975, 1978, 1979) were attributed to an increase in bleeding time and changes of platelet aggregation after dietary intake of *n*-3 PUFA contained in FO. More recent publications, however, report no (Swails *et al.* 1993) or only clinically irrelevant (Rogers *et al.* 1987) changes in platelet aggregation.

Because of beneficial effects on the outcome of severely ill patients (Bastian *et al.* 1998; Gadek *et al.* 1999) and the controversial issue of haemostasis during *n*-3 PUFA administration (Knapp, 1997) the current study was designed to investigate whether supplementation of total parenteral nutrition (TPN) with FO affects platelet function and plasma haemostatic factors in patients after elective major gastrointestinal surgery. Differential effects on intrinsic and extrinsic activation of the coagulation system were investigated by observation of the activated factors VII and XII.

Materials and methods

Patients

With institutional review board approval and patient written informed consent, forty-four patients suffering from carcinoma of the gastrointestinal tract or pancreas were prospectively enrolled. Elective surgery (Table 1) was performed between May 1999 and February 2000. Post-operatively the patients were observed for 5 days either in the thirteen bed intensive care unit (ICU) of the Department of Anaesthesiology or in the sixteen bed surgical ICU. All patients were postoperatively extubated, spontaneously breathing and received TPN for 5 days. After inclusion in this study, the patients were randomly assigned to receive either TPN supplementation with SO or TPN supplementation with SO + FO (Table 2). Inclusion of patients to the

Table 2. Composition of the lipid emulsions

		Lipovenoes® 10% PLR (g/l) Refined soy bean oil (SO)	Omegaven® 10% (g/l) Refined fish oil (FO)
EPA	C20 : 5 <i>n</i> -3	—	12.5–28.2
DHA	C22 : 6 <i>n</i> -3	—	14.4–30.9
Myristic acid	C14 : 0	0.06	1.0–6.0
Palmitic acid	C16 : 0	12.00	2.5–10.0
Palmitoleic acid	C16 : 1 <i>n</i> -7	—	3.0–9.0
Stearic acid	C18 : 0	4.00	0.5–2.0
Oleic acid	C18 : 1 <i>n</i> -9	22.42	6.0–13.0
Linoleic acid	C18 : 2 <i>n</i> -6	46.1–55.7	1.0–7.0
Linolenic acid	C18 : 3 <i>n</i> -3	4.8–10.6	≤2.0
Stearidonic acid	C18 : 4 <i>n</i> -3	—	0.5–4.0
Eicosaenoic acid	C20 : 1 <i>n</i> -9	—	0.5–3.0
Arachidonic acid	C20 : 4 <i>n</i> -6	—	1.0–4.0
Docosaenoic acid	C22 : 1 <i>n</i> -9	—	≤1.5
DPA	C22 : 5 <i>n</i> -3	—	1.5–4.5
Other fatty acids		—	10.51

Table 3. Regimen of total parenteral nutrition

Day	Both Groups		SO	SO + FO
	Glucose (Glucosteril 40 %)	Amino acids (Aminosteril KE 10)	Lipids (Lipovenoes® 10 % PLR)	Lipids (Lipovenoes® 10 % PLR) (Omegaven® 10 %)
1	2.0 g/kg per d	0.5 g/kg per d	0.8 g SO/kg per d	0.64 g SO/kg per d +0.16 g FO/kg per d
2–5	3.0 g/kg per d	1.2 g/kg per d	1.0 g SO/kg per d	0.8 g SO/kg per d +0.2 g FO/kg per d

respective groups was achieved by computer derived block randomisation. Solutions were prepared in the central pharmacy of the university hospital, delivered blinded to the ICU, and further handled by a nurse who was unaware of the study protocol. The investigators were, thus, blinded to the infused drug. On the preoperative day (day -1) baseline values were obtained and again on the first postoperative day (day 1), before TPN was started.

Interventions

All patients received TPN for 5 days postoperatively according to Table 3 by an indwelling central venous 3 lumen catheter. Glucose (Glucosteril 40 %, Fresenius-Kabi, Bad Homburg, Germany), amino acids (Aminosteril 10 %, Fresenius-Kabi) and a soybean oil emulsion (Lipovenoes® 10 % PLR, Fresenius-Kabi) were provided to both groups by means of infusion pumps (Volumed µVP5000, Fresenius-Kabi, Bad Homburg, Germany). In the FO-group, however, the *n*-6 lipid content of TPN was partially replaced by *n*-3 PUFA (Omegaven®, Fresenius-Kabi) up to 0.2 g/kgBW per day, which is the maximum recommended daily Omegaven® dosage. Moreover all patients daily received fat- (Vitalipid, Pharmacia, Erlangen, Germany) and water soluble vitamins (Soluvit, Pharmacia) as well as trace elements (Addel N, Pharmacia).

Blood samples

In addition to the routine laboratory measurements, including peripheral blood cell counts and biochemical analysis, 2 ml of citrated whole blood were obtained at 08:00 daily for resonance thrombography. Plasma for analysis of the coagulation factors VIIa and XIIa was separated and kept deep frozen at -80°C until measurement.

Routine coagulation parameters

The coagulation parameters thromboplastin time (Quick), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin (AT) III and platelet counts were quantified in the Department of Clinical Chemistry, University Hospital of Dresden, Germany, according to standard procedures. Reference values were: Quick (70–120 %), aPTT (30–40 s), fibrinogen (1.5–4.6 g/l), AT III (80–120 %) and platelet counts (150–400 Gp/l).

Factor VIIa

A test kit (Stacot VIIa-rTF, Diagnostica Stago, Parsippany, NJ, USA) for the determination of activated Factor VII in citrated plasma was used according to the manufacturers specifications. The recombinant soluble tissue factor (rsTF) holds a cofactor function specific for factor VIIa, in the presence of factor VIIa, phospholipids and Ca⁺⁺ the rsTF initiates coagulation of plasma. In this system the observed clotting time bears an inverse relationship with the factor VIIa level initially present in the plasma being tested. The rsTF does not activate factor VII into factor VIIa; consequently the factor VII present in the test plasma does not interfere in the assay.

Factor XIIa

For the quantitative detection of activated factor XII in plasma an immunoassay (Progen Biotechnik, Heidelberg, Germany) was used according to the manufacturer's specifications. The wells of the XIIa microtiter strips are coated with mouse monoclonal antibodies specific for XIIa. During the first incubation XIIa will bind to the immobilised antibody. After removal of unbound plasma components, a conjugate of enzyme labelled polyclonal sheep antihuman XIIa antibody binds to surface bound antigen. Following development with substrate solution absorbance is measured at 550 nm. Reference values for healthy volunteers: 1.7–2.3 ng/ml.

Resonance thrombography (RTG)

RTG was performed with an RTG-analyser (CS-3, Amelung, Lemgo, Germany) according to the manufacturer's specifications from 250 µl of citrated whole blood to which 150 µl of CaCl₂ (25 mmol/l) were added. Coagulation is mechanically activated in whole blood according to physiological conditions of blood current and intravascular shear stress. Measuring coagulation on the basis of the resonance effect induced by the elastic fibrin structure the RTG principle (Hartert, 1981) is different from thrombelastographs (Mischke, 2000). Information about velocity and quality of clot formation is given by a specific graph. Distinct segments of the RTG plot represent fibrin formation (*f*-time=duration of upward slope) or platelet function (*p*-time=duration of downward slope). RTG *p*-time reflects functionality of platelet derived coagulation, regardless of the underlying cause of platelet malfunction (low platelets, uraemia, fibrinogen cleavage products).

Statistics

Data are presented as arithmetic mean (SD). Differences of single measurements between groups were tested with Student's *t*-test or Chi square test. Repeated measurement analysis within and between groups was achieved with general linear model (GLM). Pre TPN values were considered as covariates during statistical analysis. Significance was accepted at $P < 0.05$. Analysis was performed using SPSS for MS Windows (Release 10.0.7, SPSS, Chicago, IL).

Results

Clinical characteristics of the patients

Demographic characteristics of the patients concerning age, gender, SAPS II (Le Gall *et al.* 1993) at entry, body mass index and surgical procedures are summarised in Table 1. There were no significant differences between groups at entry.

Standard coagulation parameters

Baseline values of Quick [SO: 103(15%) *v.* SO + FO 102(10%)] and aPTT [SO: 33(4 s) *v.* SO + FO: 33(4 s)] before surgery did not differ significantly between the two groups. Surgery significantly ($P < 0.001$) reduced Quick [SO: 70(14%) *v.* SO + FO: 72(8%)] and increased aPTT [SO: 47(10 s) *v.* SO + FO: 44(7 s)]. Over time there were no significant differences between groups and baseline values were regained between days 3 and 4 after surgery. During this time daily heparin administration (Liquemin, Roche, Grenzach-Whylen, Germany) was adjusted to achieve aPTT between 35 and 40 s. The required dosages of heparin were comparable in both groups and increased from day 1 [SO: 10278(3627) I.U. *v.* SO + FO: 10104(4163) I.U.] to day 6 [SO: 14583(2745) I.U. *v.* SO + FO: 13542(3825) I.U.]. Cumulative fluid balance over the 5 postoperative days did not differ significantly [SO: +4729(3340 ml) *v.* SO + FO: +4201(3368 ml); $P = 0.39$]. Postoperative levels of

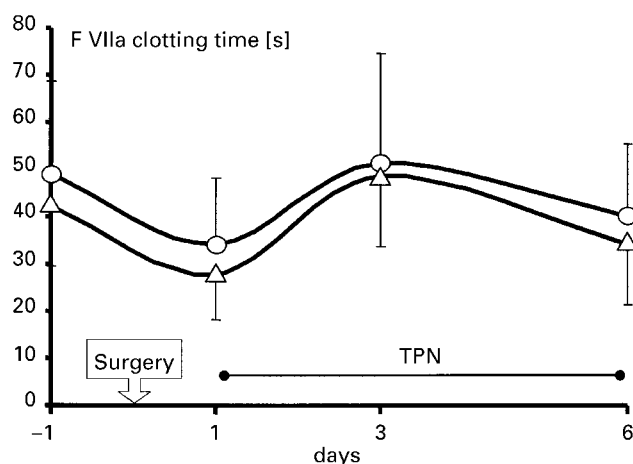


Fig. 1. Factor VIIa induced clotting time [s, mean (SD)] after major abdominal surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (Δ) or with SO + fish oil (\circ). No statistical significant between-group difference could be detected.

fibrinogen [SO: 2.3 (0.6 g/l) *v.* SO + FO: 2.2 (0.6 g/l)] and AT III [SO: 64(12%) *v.* SO + FO: 61(12%)] as well as measurements until day 6 of fibrinogen [SO: 5.5(1.3 g/l) *v.* SO + FO: 6.2(1.7 g/l)] and AT III [SO: 86(14%) *v.* SO + FO: 85(18%)] revealed no significant between-group differences.

Activated factors VII and XII

Factor VIIa dependent clotting time [(Fig. 1) preoperative: SO: 42(13 s) *v.* SO + FO: 49(19 s)] dropped postoperatively [day 1: SO: 28(9 s) *v.* SO + FO: 34(14 s)] but preoperative values were regained on day 3. Levels of factor XIIa [(Fig. 2) preoperative: SO: 2.0 (0.6 ng/ml) *v.* SO + FO: 2.2 (1.0 ng/ml)] declined to a minimum on postoperative day 3 [SO: 1.4 (0.6 ng/ml) *v.* SO + FO: 1.6 (0.6 ng/ml)]. Concentrations of both factor VIIa and factor XIIa were not significantly different between groups.

Platelet function

Platelet counts [preoperative: SO: 232(87 Gpt/l) *v.* SO + FO: 224(112 Gpt/l)] dropped during surgery [SO: 185(59 Gpt/l) *v.* SO + FO: 179(123 Gpt/l)] but regained baseline values at postoperative day 4 [SO: 205(62 Gpt/l) *v.* SO + FO: 214(78 Gpt/l)]. Platelet function (Fig. 3) as observed by RTG- p-time [preoperative: SO: 2.2(1.1 min) *v.* SO + FO: 2.6(2.4 min)] was delayed postoperatively [SO: 3.6(2.2 min) *v.* SO + FO: 4.1(2.9 min)]. At day 3 preoperative levels of platelet function were re-established. No differences in platelet counts or function were found between groups.

Complications

Bleeding complications were comparably low in both groups. Preoperatively measured haemoglobin concentrations [SO: 7.4(1.2 mmol/l) *v.* SO + FO: 7.9(1.6 mmol/l)] declined during surgery [SO: 7.2(1.1 mmol/l) *v.*

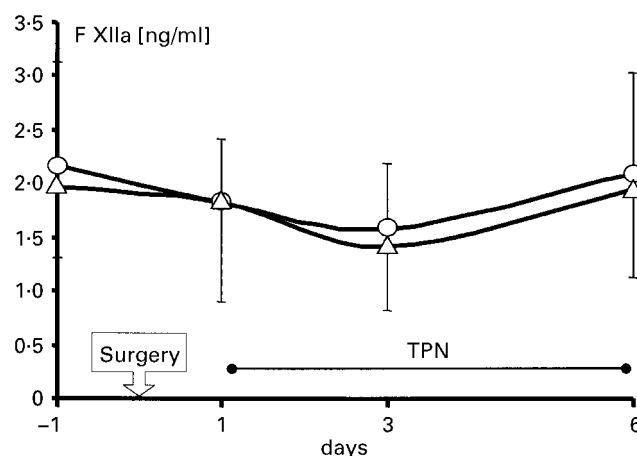


Fig. 2. Activated factor XII levels [mean ng/ml (SD)] after major abdominal surgery followed by total parenteral nutrition (TPN) supplemented with soybean oil (Δ) or with SO + fish oil (\circ). No statistical significant between-group difference could be detected (GLM).

SO + FO: 6.6(1.1 mmol/l)]. Minimum values were reached at day 3 [SO: 6.3(0.6 mmol/l) v. SO + FO: 6.0(0.9 mmol/l)]. GLM-analysis revealed no differences between the groups ($P=0.41$). Postoperatively transfused amounts of packed red blood cells [SO: 317(787 ml) v. SO + FO: 325(405 ml)] showed no difference between SO and SO + FO groups. Administration of fresh frozen plasma (FFP) during TPN, however, was more frequent in the SO group [156(311 ml)] compared with SO + FO [42(167 ml)] but the difference did not reach statistical significance ($P=0.17$). Mean total hydroxyethyl starch 10% 250/0.5 administration was higher in the SO + FO group [3458(1565 ml) v. SO: 2750(1328 ml)], but no level of significance was reached.

Discussion

During the past decades intensive collaborative research in the fields of chronic and acute inflammatory disorders has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. In the early phase of inflammation interleukins and lipid-mediators are excessively released and play a crucial role in the pathogenesis of organ dysfunction (Heller *et al.* 1998). Arachidonic acid (AA) is the precursor of the pro-inflammatory eicosanoids, and is released from membrane phospholipids in the course of inflammatory activation and subsequently metabolized to prostaglandins and leukotrienes. Various strategies have been evaluated to control the excessive production of lipid mediators, such as inhibition of phospholipase A₂, the enzyme catalysing AA release, the blockade of cyclooxygenase- and lipoxygenase enzymes as well as the development of receptor antagonists against platelet activating factor and leukotrienes.

Encouraging results on a variety of outcome parameters were obtained in critically ill patients by supplementation with long chain n-3 fatty acids, as part of an enteral nutrition regimen (Bower *et al.* 1995; Bastian *et al.* 1998; Gadeck *et al.* 1999). In states of inflammation, EPA is released to

compete with AA for metabolism inducing the production of less inflammatory and less chemotactic derivatives.

Because n-3 PUFA containing lipid emulsions are now available for intravenous administration to humans, the current study was designed to address the controversial subject of haemostasis (Rogers *et al.* 1987; Swails *et al.* 1993; Knapp, 1997) during the maximum recommended FO dosage (0.2 g/kg per day) in terms of plasmatic haemostasis and platelet function after major abdominal surgery. The setting of surgical trauma and TPN was chosen to assure intravascular availability of the fatty acids, which could not be guaranteed in the situation of enteral nutrition in which gastrointestinal transport and mucosal uptake function could confound measured parameters.

In this study patients undergoing major abdominal surgery were enrolled. The two groups were comparable regarding standard demographic characteristics and surgical trauma (Table 1). Classical haemostasis parameters such as Quick, aPTT, platelet counts and AT III were measured prior to surgery and before start of TPN at postoperative day 1. These values varied as expected after a major abdominal surgical procedure, indicating a moderate activation of coagulation, without significant differences between the two study groups. During the postoperative observation period, however, preoperative coagulation capacity was regained regardless of the type of PUFA administered.

While n-3 PUFA modulate cytokine expression (Endres *et al.* 1989; Molvig *et al.* 1991; Chandrasekar & Fernandes, 1994) PUFA-dependent effects on tissue factor (TF) expression and the extrinsic coagulation pathway were further differentiated by means of quantification of activated factor VII. When TF is presented to plasma components during vascular injury, extrinsic coagulation is activated. Factor VIIa and its cofactor TF assemble on a negatively charged membrane surface in a Ca²⁺-dependent manner to form an enzyme complex which proteolytically converts factor X to Xa (Bach, 1988). As depicted in Fig. 1 surgical trauma accelerates factor VIIa-induced clotting, reflecting an elevated level of activated factor VII and a postoperative (day 1) hypercoagulatory extrinsic state. Fish oil administration at the concentration used in this study, however, does not seem to interfere with TF/VIIa activation.

The influence of fatty acid administration on intrinsic coagulation were investigated by measurement of activated factor XII (Fig. 2), which is a component of the contact system of blood coagulation which also includes prekallikrein, HMW kininogen and factor XI. Because the main physiological activators of factor XII include fatty acids and the surface of certain types of lipoprotein particles (Mitropoulos *et al.* 1989), analysis of factor XIIa during differential PUFA administration was of special interest. In contrast to the effect on extrinsic factor VIIa, surgical trauma was of minor influence for intrinsic factor XIIa levels. Moreover, differential PUFA administration had no impact on XIIa formation.

As expected no differences in platelet counts were observed among the study groups. Platelet function, however, as analysed by RTG did not differ either (Fig. 3). Reduced levels of platelet activating factor (PAF) due to n-3 PUFA, as reported by Sperling *et al.* (1987) might, thus, be of minor impact in the current clinical setting. Postoperative

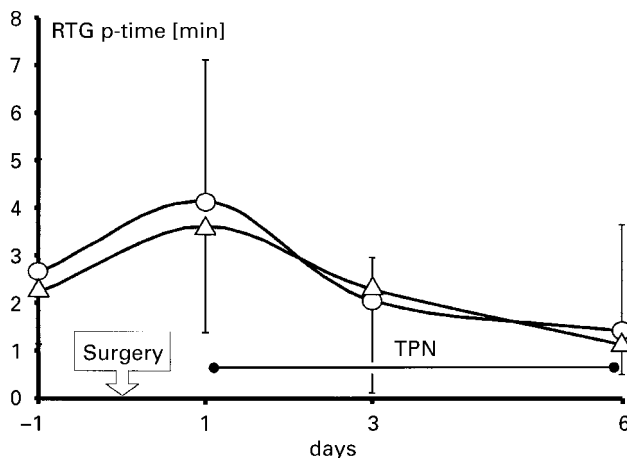


Fig. 3. Downward slope period (min) in resonance thrombography (RTG)=platelet induced clot retraction (p)-time [mean (SD)], after major abdominal surgery followed by total parenteral nutrition (TPN) supplemented soybean oil (Δ) or with SO + fish oil (○). No statistical significant between-group difference could be detected.

delay in RTG *p*-time might reflect dilution effects due to intravenous fluids.

Global parameters for the estimation of the quality of coagulation and haemostasis such as haemoglobin levels or the demand for packed red blood cells were in accordance to coagulation parameter measurement and were independent of differential PUFA administration. The underlying cause for insignificant higher need of fresh frozen plasma in the SO-group cannot be answered from the laboratory measurements and might reflect physician decisions being based upon the individual clinical aspect, rather than on laboratory values. The mean total amount of hydroxyethyl starch was insignificantly higher in the SO + FO-group. A more extensive intraoperative administration of hydroxyethyl starch solution which accounted for that difference had minor impact on coagulation.

Summarising our results, fish oil administered up to 0.2 g/kg per day, was shown to be safe in terms of intrinsic and extrinsic coagulation and did not influence platelet aggregation. Regarding the beneficial effects in critically ill patients, attributed to *n*-3 PUFA, which are covered by a variety of studies, enteral or parenteral nutrition with these nutrients should be considered as a part of anti-inflammatory immunonutrition.

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