Impact of the ratio of intravenous omega-3 vs. omega-6 polyunsaturated fatty acids in postoperative and in septic patients—A *post hoc* database analysis

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Introduction

Administration of omega-3 fatty acids (FA) contained in fish-oil (FO) has been shown to reduce morbidity and mortality in both, postoperative[1,2] and critically ill patients,[3,4] without undesired side effects on clinical haemostasis.[5] Underlying effects are altered lymphocyte and phagocyte functions[6,7] as well as modulation of lipid mediator generation[8] and gene expression.[9,10]

We recently identified dose-related effects of omega-3 FA on risk adjusted outcome in the present database of 661 patients.[11] Intravenous (i.v.) fish oil doses exceeding 50 mg/kg/d corresponding with cumulative doses of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) of 22 mg/kg/d were significantly associated with a reduction of both length of ICU and hospital stay. Moreover, necessity for antibiotic treatment was significantly lower when FO doses between 150 and 200 mg/kg/d (65–86 mg/kg/d EPA+DHA) were infused. Survival was significantly improved with i.v. doses of 100–200 mg/kg/d (43–86 mg/kg/d EPA+DHA) as compared to doses <50 mg/kg/d (<22 mg/kg/d EPA+DHA). Further, we identified FO doses corresponding with a maximum beneficial effect with regard to the underlying diseases and showed lowest ICU length of stay at a i.v. FO dose of 230 mg/kg/d in patients with abdominal sepsis and peritonitis, corresponding with an EPA+DHA dose of 99 mg/kg/d. Prospective randomized data from septic patients reported by Pontes-Arruda who showed improved survival and reduced secondary organ failure when 170 mg/kg/d of omega-3 FA were administered via the *enteral* route[4] are in line our findings.

Experimental data exist substantiating the hypothesis that most favourable outcome in peritonitis[12] or immunosuppression[13] should be obtained when the ratio of omega-3 vs. omega-6 FA ratio is close to 1:2. Accordingly, Morlion reported peak leukotriene C_5/C_4 ratios in postoperative patients when a omega-3/omega-6 FA ratio of 1:2 was administered at a total fat load of 1 g/kg/d, therefore identifying a maximum metabolic efficacy of omega-3 FA.[14] A meta analysis in a chronic disease setting[15] showed that the tissue ratio of arachidonic acid/EPA was a poor predictor for coronary artery disease as opposed to the sum of DHA+EPA incorporated into tissue. Thus, it remains controversial if besides absolute amounts the omega-3/omega-6 FA ratio is of outcome relevance in distinct settings.

Both, FO and soya bean oil (SO) emulsions contain omega-3 and omega-6 FA in defined ratios (FO 7.5:1 and SO 1:6.5) which can be calculated from FO and SO doses for the individual patient. Moreover, medium chain triglycerides (MCT) modulate the infused lipid pattern by increasing the non-omega-3/non-omega-6 FA load and may improve liver function in critical illness.[16] In the present database re-evaluation we hypothesized that variations of the omega-3 vs. omega-6 FA ratio also considering MCT emulsions may affect outcome in critically ill patients, independent from the underlying absolute dosage of EPA+DHA.

Patients and methods

Detailed patient characteristics and specific interventions have been published previously.[11] Briefly, the present study included 661 patients in 82 German hospitals with a maximum of 10 patients recruited per hospital. Patients were enrolled who had total parenteral nutrition including FO (Omegaven-Fresenius 10%, Fresenius-Kabi, Bad Homburg, Germany) for at least 3 consecutive days regardless of the underlying diagnosis. FO-doses and n3/n6 ratios resulting from the parallel infusion of soybean oil emulsion were to the discretion of the attending physician. The sample included 255 patients after major abdominal surgery, 276 with peritonitis and abdominal sepsis, 16 with non-abdominal sepsis, 59 after multiple trauma, 18 with severe head injury, and 37 with other diagnoses. Risk-adjusted length of stay and use of antibiotics, as well as mortality were analyzed with respect to the primary diagnosis.

Antibiotic demand was defined as additional long term (>3 d) antibiotic treatment during ICU stay exceeding one intraoperative single shot with a 2nd generation cephalosporine. In the group of peritonitis/abdominal sepsis patients with pancreatitis, intestinal diverticulitis or M. Crohn intestinal fistula without long-term antibiotic treatment were, likewise, included and were equally distributed over the n3/n6 ratio groups, explaining that not all of these patients received antibiotics.

Based on the individual composition of the infused lipid emulsions we calculated the daily EPA+DHA doses as well as the ratio of omega-3 and omega-6 FA for each patient from the cumulative amounts of infused FO, SO, and mixtures of medium and long chain triglycerides (MCT/LCT).

Statistics

Descriptive data are given as arithmetic mean $\pm$ standard deviation (text and Table 2). In risk adjusted data (Table 1 and Figure 2) the measure of scatter is standard error of means. The mean risk adjusted ICU stay was compared between omega-3/omega-6 FA ratio subgroups using linear models with the quantitative covariables age, body mass index, the SAPS II score, daily calorie intake and the binary covariable death. Impact of MCT/LCT emulsions were calculated accordingly.

Due to the *post-hoc* analysis of the data theoretically selection bias could have occurred, which invalidates the results and which does not allow any serious interpretation of the data. Thus risk adjustment for all reported outcome parameters by covariate analysis of variance (CANOVA) was performed. This procedure eliminates heterogeneities between the analyzed subgroups by introducing potentially confounding factors as covariates. Whether or not one factor is influencing between-group comparisons is checked by a foregoing multivariate regression analysis. Significant factors identified by this procedure are considered as confounders and have to be introduced into the statistical model to eliminate selection bias. CANOVA adjusts the *a priory* risk derived from defined factors for all groups to a common level and thus, enables, comparisons. This was done for all parameters.

Multiple comparisons are Sidak-adjusted. Approximate normal distribution of the analysis variables were graphically checked by box plots. Standardized beta coefficients ($s\beta$) deriving from linear regression analysis were applied to compare the individual impact of each of the two factors

Table 1 Length of hospital and ICU stay (mean±SEM) in total population regarding individual omega (n)-3 vs. n6 ratio.

n3/n6 ratio	*n*	EPA+DHA dose (mg/kg/d)	ICU stay (d)	Hospital stay (d)
7.5:1	32	60±2	15.3±2.5	32.9±3.3
1:1	39	62±3	19.5±2.2	34.3±2.9
1:2	170	61±1	14.6±1.1	29.8±1.4
1:3	272	56±1	11.0±0.8*	28.9±1.1
1:4	127	49±1	10.1±1.3*	26.2±1.7

CANOVA comparisons adjusted for SAPS II score, age, survival, calorie intake, FO dose and alpha inflation (Sidak).
*$p<0.01$ vs. n3/n6 ratio 1:1.

EPA+DHA dose [mg/kg/d] and omega-3/omega-6 FA ratio on outcome.

Results

From 661 recruited patients (377 male, 284 female) 640 datasets were eligible to calculate n3/n6 ratios and to perform complex statistics. Patients were 62.8±16.5 years old, had a SAPS II score of 32.2±13.6, a body mass index of 25.1±4.2 kg/m^2 and received a dose of EPA+DHA 56±16 mg/kg/d (SD). Both, EPA+DHA dosage and n3/n6 ratio significantly affected length of ICU stay in a linear regression model (Figure 1). When comparing the independent impact of each of the two factors regarding standardized beta coefficients omega-3 FA dosage ($s\beta = 0.240$) has higher factor weight as the omega-3/omega-6 FA ratio ($s\beta = -0.185$). FO had most favorable effects on length of ICU stay for the total study population when the omega-3/omega-6 FA ratio was <1:2 (Table 1). While patients with abdominal sepsis had a significantly shorter risk adjusted ICU stay at omega-3/omega-6 FA ratios of 1:2–1:4 as compared to a ratio of 1:1 this difference could not be detected in postoperative patients (Figure 2).

No difference in antibiotic demand was observed in the total population and in postoperative patients. Patients with abdominal sepsis receiving a omega-3/omega-6 FA ratio of 7.5:1 (pure 10% FO emulsion) antibiotic demand was reduced to 50% ($p<0.001$) as compared to all other ratios (Table 2). No difference in risk- and FO dose-adjusted mortality was found with respect to the omega-3/omega-6 FA ratio. No effect on risk adjusted antibiotic demand or mortality was found regarding the use of non-FO-based MCT/LCT emulsions.

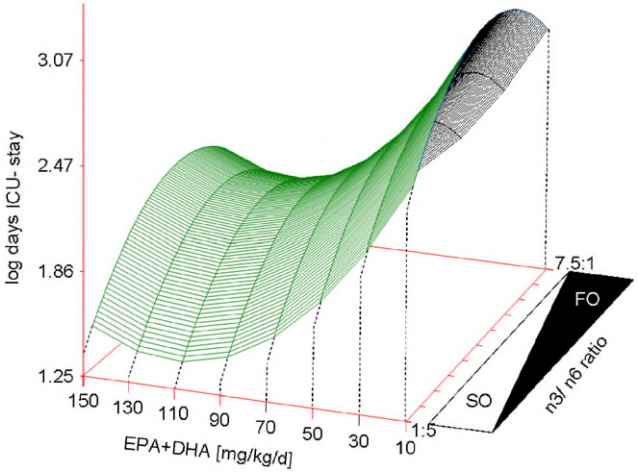

Figure 1 Surface of the predicted outcome ICU stay over the two variables eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) dose and ratio omega (n)3/n6.

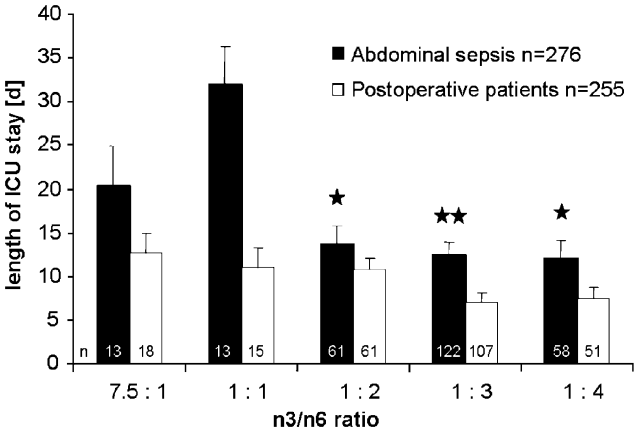

Figure 2 Risk adjusted length of ICU stay (mean and SEM) in omega (n)-3/n6 ratio subgroups in patients with abdominal sepsis and in postoperative patients. CANOVA comparisons adjusted for SAPS II score, age, survival, calorie intake, FO dose and alpha inflation (Sidak). **$p<0.001$; *$p<0.01$ vs. group 1:1.

Discussion

Evidence on experimental grounds,[17] from large case series[11] and from first prospective randomized trials[4,18] point towards the possibility that organ function and survival may be improved by administration of omega-3 FA, even in critically ill patients. However, optimum dosing and the best ratio of n3/n6 FA with regard to the underlying diagnosis and disease severity remains speculative.

Experimental and preliminary clinical data suggesting unique biochemical effects of the omega-3 vs. omega-6 FA ratio in peritonitis,[12] during immuno-suppression[13] or in postoperative patients,[14] when adjusted to 1:2. Scientifically, the ratio of omega-3/omega-6 FA appears as a imprecise and easily misunderstood metric. It does not distinguish between (a) long and short chain EFAs, and (b) masses of EFA. Even if precisely defined (e.g, LA/ALA ratio, or AA/EPA ratio) the

Table 2 Descriptive statistics (not risk adjusted) on clinical outcome data (mean±SD) of all subpopulations regarding individual omega (n)-3 vs. n6 ratio.

n3/n6 ratio	*n*	28-day mortality (%)	Predicted SAPS II mortality (%)	ICU stay (d)	Hospital stay (d)	Antibiotic demand (%)
Abdominal sepsis, peritonitis						
7.5:1	13	7.7	12.2±15.5	13.4±24.6	30.4±23.9	50.0^{+++}
1:1	13	0	20.1±23.4	29.3±28.9	45.0±28.6	100
1:2	61	8.2	21.7±15.2	12.9±13.5*	28.9±19.5	93.4
1:3	122	11.5	22.8±16.6	12.7±14.4**	29.9±20.2	91.7
1:4	58	5.2	22.2±17.2	14.1±18.8*	28.1±20.7	94.7
Postoperative patients						
7.5:1	18	0	4.9±2.1	9.2±7.22	25.9±9.8	77.8
1:1	15	0	14.9±21.2	11.4±12.6	25.6±12.9	73.3
1:2	61	8.2	8.8±11.9	11.5±15.7	27.4±15.3	70.5
1:3	107	7.5	8.0±10.8	7.3±7.1	27.7±11.1	67.3
1:4	51	3.9	5.7± ±6.0	7.1±7.8	27.5±14.3	80.0
Multiple trauma						
7.5:1	0	n.a.	n.a.	n.a.	n.a.	n.a.
1:1	1	0	79.9	22.0	72.0	100
1:2	17	11.8	41.3±21.8	32.4±25.9	46.5±26.6	64.7
1:3	24	0	42.1±28.7	19.5±15.8	37.0±33.9	91.3
1:4	13	7.7	52.6±27.3	15.±11.7	29.0±21.7	84.6
Non abdominal sepsis						
7.5:1	0	n.a.	n.a.	n.a.	n.a.	n.a.
1:1	4	25.0	16.3±10.4	12.7±7.7	25.1±20.7	100
1:2	6	0	21.5±12.9	22.8±15.7	39.1±17.1	100
1:3	2	0	35.9±1.6	24.5±14.8	54.5±2.1	50.0
1:4	2	50.0	26.0±31.6	6.5±2.1	19.4±4.1	100
Severe head injury						
7.5:1	0	n.a.	n.a.	n.a.	n.a.	n.a.
1:1	1	0	70	10.0	39.0	100
1:2	9	0	57.7±12.1	17±8.3	26.1±12.3	88.9
1:3	8	0	45.0±20.4	10±7.3	12.2±9.7	28.6
Others						
1:4	0	n.a.	n.a.	n.a.	n.a.	n.a.
7.5:1	1	0	30.6	10.0	43.0	100
1:1	5	0	6.1±3.5	15.8±5.8	19.2±3.8	100
1:2	16	12.5	15.9±17.8	11.8±8.3	20.0±8.7	93.8
1:3	9	11.1	4.9±3.7	6.3±3.8	17.5±5.6	66.7
1:4	3	0	9.6±13.0	5.5±0.7	31.0±31.1	100

Due to the size of subgroups statistics were only performed for postoperative patients and abdominal sepsis. CANOVA comparisons adjusted for SAPS II score, age, survival, calorie intake, FO dose and alpha inflation (Sidak).
n.a. not applicable.
$^{*}p<0.01$ vs. n3/n6 ratio 1:1.
$^{**}p<0.001$.
$^{+++}p<0.001$ vs. all other n3/n6 ratios.

problem of amounts remains. As we found dose-related outcome effects of fish oil in our database we wondered if ratio-related effects would, likewise, be detectable as reported previously.[12–14] We recalculated our data to take into account that both, FO and SO emulsions contain omega-3 and omega-6 PUFA in a predefined ratio and that 45% of patients received MCT emulsion. Admixture of FO, SO and MCT, however, was to the discretion of the attending physician and therefore the n3/n6 ratio was variable at given dosages of EPA and DHA.

Controlled studies to systematically explore the effects of varying ratios or amounts of omega-6 and omega-3 PUFAs aiming to show that, either at a fixed daily dose of omega-3 PUFA, increasing amounts of omega-6 PUFA lead to worse outcome or to show that increasing amounts of omega-3 PUFA infused on a stable background of omega-6 PUFA is

associated with benefit, would always be hampered by the problem that the dose of omega-3 PUFA would be fixed to the omega-3/omega-6 ratio and, thus, the observed effects could be assigned to neither of both factors dose or ratio. Therefore, analysis of the present dataset despite its limitations due to the observational character is able to detect independent effects of both factors by using complex statistics.

This database re-calculation now yielded additional aspects of our previous FO-dose-based study,[11] which are particularly relevant when tailoring lipid emulsions for parenteral nutrition. On introduction of omega-3 FA lipid emulsions into the European market n3/n6 composition-ratios and recommendations on dosage were based on assumptions from few experimental data and remained since then widely unchanged. Consequently continuing this practice will not allow to find optimum dosages and ratios in the future. The large database of this study contains a wide range of independently varied dosages and ratios and, thus, despite its observational character, gives potential valuable information on their optimum levels with regard to clinical outcome, as risk adjusted statistical procedures are applied.

Effects related to the omega-3/omega-6 FA ratio on risk-adjusted length of ICU-stay may be confounded by the individual dose of omega-3 FA as well as by patient factors such as age and disease severity and tolerance of parenteral nutrition. Thus, patient age, SAPS II score and daily calorie load as well as the dose of omega-3 FA were introduced into univariate statistical analysis as co-variates and were, therefore controlled.

Regression analysis and data from Table 1 suggest that it is not only the factor daily dosage of DHA and EPA affecting outcome as previously reported.[11] Rather, both factors, n3-dose and n3/n6 ratio have statistical significant impact on outcome independently from each other and with distinct factor weight. The n3/n6-ratio had the largest impact in patients with pro- inflammatory triggered disease, such as sepsis as opposed to postoperative patients (Figure 2). The lower risk-adjusted antibiotic demand in septic patients receiving an omega-3/omega-6 FA ratio of 7.5:1 ($p<0.001$) was statistically not significantly associated with shorter ICU stay. The patients in this group predominantly received omega-3 FA, not omega-6 FA, known to be beneficial on inflammatory mediator production.[19] In this regard we previously reported that doses of 150–200 mg/kg/d FO (65–86 mg/kg/d EPA+DHA) are associated with lower antibiotic demand.[11] Thus, the cause of missing statistical significance levels in length of ICU stay is most likely a problem of the case load in this subgroup. To detect a statistical significant difference at the same level of variation 33 patients per group would have been necessary.

The use of MCTs was allowed in the study and their effect on outcome was additionally analyzed. Firstly univariate statistics was carried out, further they were introduced into multivariable statistical models. No significant effects from MCT administration could be detected on our endpoints in univariate statistics. They, likewise, did not significantly contribute to our multivariate models. Bias produced by MCTs was thus, mathematically controlled.

Experimental data of Pscheidl et al.[20,21] and Kelbel et al.[22] support the observation, that fish oil improves both splanchnic perfusion and intestinal lymph node as well as liver killing capacity of bacteria and, thus, might prevent infection. These immune-augmenting effects of fish oil might, likewise, contribute to the significantly reduced mortality as compared with the SAPS II predicted mortality (Table 2). Several causes may account for the failure of the present analysis to detect effects of the omega-3/omega-6 FA ratio on survival. First, despite the fact that the omega-3/omega-6 FA ratio had a significant impact on outcome it was less than the substantial clinical effect of omega-3 FA *dosage*. Thus, effects deriving from the omega-3/omega-6 FA ratio may not excel those of the factor dosage as reported earlier.[11] Second, a brief single nutritional intervention is unlikely to produce extensive effects on patient outcome in postoperative patients having a low mortality risk. Third, incorporation of lipids into cell membranes may vary inter-individually, explaining the variability of these results.

The statistically significant results are derived from a small group of patients given PUFA at the ratio of 1:1. The results from a small subgroup might be prone to selection bias. These 39 patients were recruited from 19 different hospitals with a mean of 2.1 ± 1.6 patients per hospital. Thus, ICU tradition and patient mix may be assumed to be equally distributed and are very unlikely to have affected outcome.

Despite a beneficial association between the administration of omega-3 FA and outcome it must be kept in mind that the present study was observational without *a priori* defined dosages, n3/n6, MCT/LCT ratios and without a control group (points that have been thoroughly discussed in the primary paper[11,23]). From the view point of study design the absence of *a priori* defined doses clearly flaws conclusions from the current data. The observational character of this study, thus, merely allows hypothesis generating conclusions, not however, dose recommendations. However, performing a study with defined doses and ratios of n3/n6 FA fixes both factors and, thus, the observed effects could not be assigned to dose or ratio. Therefore, the present observational study in a greater number of patients with free variations in both factors (doses and ratios) by the attending physicians enables detection of independent effects and optima of both factors by using complex statistics. The level of evidence generated by our study is, however, lower than this of a prospective randomized study. Reliability of the present *post hoc* database analysis for daily clinical practice of intensive care physicians is, thus, limited. Hence, recommendations on dosages or ratios for daily practice cannot be derived from this work, rather, prospective randomized studies have to prove the value of omega-3 FA in critical care medicine. In this regard, recently published work of Pontes-Arruda et al.[4] confirm our data with respect to the dosages and n3/n6 ratios in the subgroup of septic patients.

In conclusion optimal omega-3 FA administration is not only dose-related but is also independently affected by the ratio of omega-3/omega-6 FA. The largest benefit may be expected from i.v. FO in abdominal sepsis at a given dose of EPA+DHA at a omega-3/omega-6 FA ratio of $\leqslant$1:2.

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ARH carried out the studies and data analyses and drafted the manuscript. SS carried out the studies and data analyses SNS, MGA and TK conceived of the study, and participated in its design and coordination and helped to draft the manuscript. RK performed the statistical analysis and participated in the draft of the manuscript. All authors read and approved the final manuscript.

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