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Opinion paper

Intravenous fish oil in critically ill and surgical patients – Historical remarks and critical appraisal

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SUMMARY

The purpose of this review is to explain the historical and clinical background for intravenous fish oil administration, to evaluate its results by using a product specific metaanalysis, and to stimulate further research in the immune-modulatory potential of fish oil. Concerning the immune-modulatory effects of fatty acids, a study revealed that ω-3 as well as ω-6 fatty acids would prolong transplant survival, and only a mixture with an ω-6:ω-3 ratio of 2.1:1 would give immune-neutral results. In 1998, the label of a newly registered fish oil emulsion also acknowledged this immune-neutral ratio in conjunction with ω-6 lipids. Also, two fish oil-supplemented fat emulsions, registered in 2004, used a similar ω-6:ω-3 ratio. Such an immune-neutral ω-6:ω-3 ratio denoted progress for most patients compared to pure ω-6 lipid emulsions. However, this immune-neutrality might on the other hand be responsible for the limited positive clinical results gained so far in critically ill and surgical patients where in most cases significance could only be shown for the pooled effect of numerous trials. Our product specific metaanalysis also did not reveal any differences, neither in infections rates nor in ICU or hospital length of stay. To evaluate the immune-modulatory effect of fish oil administered alone, new dose finding studies, reporting relevant clinical outcome parameters, are required. Precise mechanistic or physiological biomarkers for the indication of such a therapy should also be developed and validated.

1. Introduction

In the 1970s and 1980s, epidemiologic studies revealed a lower incidence and prevalence of myocardial infarction, asthma, type I diabetes mellitus, thyrotoxicosis, multiple sclerosis, and psoriasis in Inuits [1] as well as less coronary heart disease in Japanese [2,3] populations. A higher dietary consumption of fish oil with a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was revealed as a possible cause [4,5]. In the following decade this finding stimulated trials on oral fish oil supplementation in patients with cardiovascular disease, with rheumatoid arthritis, inflammatory bowel disease, asthma or psoriasis, respectively (reviewed in Ref. [6]).

Besides the oral supplementation of fish oil for various diseases, it was also speculated that an intravenous application might have faster and better results because intravenously applied fatty acids are directly incorporated into the cell membrane in a shorter time. So, in the 1990s, case reports and phase III trials of a new intravenous fish oil emulsion (then called Omegavenös®, later Omegaven®, Fresenius Kabi, Germany) were reported, applying this emulsion as a stand-alone therapy. Grimminger et al. [7] performed a single-center trial in 20 patients with chronic plaque-type psoriasis. Patients were randomized to receive either 100 ml/day of the 10% fish oil emulsion or conventional ω-6 lipid emulsion over 10 days. Compared to the control group, which showed no significant change, a significant decrease from baseline in all disease severity score systems (ranging between 45% and 76%) was observed in the treatment group. In a later multi-center trial in 83 patients the dose was increased to 200 ml/day and the intervention time prolonged to 14 days [8]. Again, a significant decrease in the Psoriasis Area Severity Index score was observed. Grimminger et al. also infused 200 ml of 10% fish oil over nine days in a patient with moderately active colitis ulcerosa and could rapidly taper the steroid dose [9].

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The mechanisms of the immune-modulatory effects of fatty acids are manifold. They are incorporated into the cell membrane where they influence membrane structure and function. In addition, they penetrate into the cell where they impact eicosanoid and cytokine production as well as influence gene expression and cell signaling (reviewed in Ref. [10]). In summary, different fatty acids lead to a variant production of cytokines (TNFα, Interleukin-6 and Interleukin-10) as well as of prostanoids and interleukins. They also influence the cell mediated response as lymphocyte proliferation and reactivity, natural killer cell activity, neutrophil chemotaxis and phagocytosis as well as T-cell activation [10].

While the ω-6 fatty acid arachidonic acid is responsible for the production of proinflammatory prostanoids of the 2 series and leukotrienes of the 4 series, the ω-3 fatty acids EPA and DHA stimulate the production of less proinflammatory mediators of the 3 and 5 series [11]. In addition, these ω-3 fatty acids play an important role in the production of resolvins and other anti-inflammatory agents [12].

But ω-6 fatty acids also have clinically relevant immune-suppressive effects on the cellular level where they depress the above described immune reactions [10]. In 1994, an important experiment about the immunologic effects of fatty acids was reported [13]. In a model of allogenic heart transplantation, rats were postoperatively fed parenterally with different fat emulsions. The study revealed that both, ω-6 fatty acids as well as ω-3 fatty acids, significantly prolonged the transplant survival time (13.3 ± 1.0 respectively 12.3 ± 0.4 days) compared to a control group which received saline (6.7 ± 0.56 days). So, both lipid emulsions acted in an immune-suppressive way. Only a mixture of ω-6 with ω-3 in a ratio of 2.1:1 showed the same fast transplant rejection (6.7 ± 0.6 days) as a control group of animals receiving saline (7.8 ± 0.3 days). Although lacking a confirmation in humans, the authors claimed an ω-6:ω-3 ratio of 2.1:1 as appropriate for an immune-neutral lipid emulsion that would be “the optimal parenteral nutrition of ICU patients with a markedly reduced immune system” [14]. They interpreted this result as a confirmation of the hypothesis stated by Kinsella et al., in 1990 [15] in a review on dietary fatty acids, which concluded that any imbalanced intake of fatty acids with either predominant ω-6 or ω-3 fatty acids were immune-suppressive and only a balanced intake, containing ω-6 and ω-3 fatty acids in a certain ratio, would be immune-neutral, i.e. having no relevant effect on immune function.

Probably following the results of the aforementioned study [13], the recommendation of an immune-neutral ω-6:ω-3 ratio was also acknowledged in the label of Omegaven®, which was registered in March 1998. The label [16] stated that it should be used for parenteral nutrition only together with other lipid emulsions and that the part of Omegaven® should not exceed 10%–20% of the total lipid dose. Such an admixture of Omegaven® with LCT or MCT (henceforth termed “fish oil admixture”) would also guarantee an ω-6:ω-3 ratio as proposed in the study by Grimm et al. [13].

In 2004, two new premixed lipid emulsions with a fixed ω-6:ω-3 ratio (henceforth termed “fish oil-supplemented lipid emulsions”) were registered, SMOF® (Fresenius Kabi, Germany) and Lipoplus® (Lipidem® in Germany, B. Braun, Germany). Both had an ω-6 to ω-3 ratio (2.5:1 respectively 2.7:1) close to the recommendation of Grimm et al. [13] and thus can be considered balanced and immune-neutral. Table 1 lists the contents in fatty acids for the three fish oil containing lipid emulsions. For EPA and DHA only ranges are reported in the respective Summary of Product Characteristics (SMPCs) provided by the companies [16–18] or the FDA [19], due to their variation in the fish oils used for production. The table shows that not only the fish oil content varies but also the ranges of EPA and DHA differ between the products.

Table 1
EPA and DHA content in three fish oil containing formulations.

		Omegaven® 10%		SMOF® 20%		Lipoplus® 20%	
Soybean oil	g/100 ml			6		8	
Medium-chain triglycerides	g/100 ml			6		10	
Olive oil	g/100 ml			5			
Fish oil	g/100 ml	10		3		2	
		Min	Max	Min	Max	Min	Max
EPA	g/100 ml	1.25	2.82	0.20	0.70		
DHA	g/100 ml	1.44	3.09	0.20	0.70		
Sum	g/100 ml	**2.69**	**5.91**	**0.40**	**1.40**	**0.86**	**1.72**
		Min	Max	Min	Max	Min	Max
EPA	(g/10 g FO)	1,25	2,82	0,67	2,33		
DHA	(g/10 g FO)	1,44	3,09	0,67	2,33		
Sum	(g/10 g FO)	**2.69**	**5.91**	**1.34**	**4.66**	**4.3**	**8.6**

EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, FO = fish oil, Min = Minimum, Max = Maximum.
References [16–19].

Clinical results with fish oil alone, fish oil admixtures or fish oil-supplemented lipid emulsions were evaluated in various meta-analyses [20–23], most of them ending up with the conclusion that more evidence is needed from larger multi-center trials with adequate sample-size [20–22]. Significant results could only be gained for the pooled effect of essentially underpowered studies. However, to our knowledge no metaanalysis has ever evaluated clinical results in an admixture or product specific way, which is important as the supplemented emulsions have a different fish oil content (10% vs. 15%) and different ranges of EPA and DHA. The following section will therefore provide such a product specific metaanalysis.

2. Methods

For this metaanalysis, randomized controlled trials were collected from a Medline literature search including papers up to August 2016 irrespective of publication language, from previous published metaanalyses and from private literature databases of the authors. Abstracts older than 3 years not followed by a publication were omitted. Trials were agreed on by all authors. The study published by Wang et al., in 2009 [24] was suspected to include also the patients reported on in a study published by the same authors in 2008 [25]. This trial was therefore excluded for double publication. Five papers did not present standard deviations [26–29] or mean values and standard deviations [30] necessary for the calculation of the overall effect. In this case, the authors were contacted to provide the data. The metaanalyses were performed with Review Manager 5.3, the analysis model was based on random effects. Statistical significance was defined as $p < 0.05$, a trend as $p \leq 0.1$.

3. Results of the product specific metaanalysis

3.1. Effect of fish oil admixtures and fish oil-supplemented lipid emulsions on immunological parameters

Nineteen studies [24,25,27,29,31–45] with Omegaven® admixtures in critically ill patients, surgical patients, and surgical patients with malignancies applied the proposed ratio which should be expected to show rather immuno-neutral effects on the inflammatory response. Plasma concentration of TNFα were evaluated in six studies [32,37–39,42], a significant decrease was found only in two [32,37] of them. IL-6 was measured in seven trials

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