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Original article

Fish oil LC-PUFAs do not affect blood coagulation parameters and bleeding manifestations: Analysis of 8 clinical studies with selected patient groups on omega-3-enriched medical nutrition

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SUMMARY

Background & aims: The increased consumption of fish oil enriched-products exposes a wide diversity of people, including elderly and those with impaired health to relatively high amounts of n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs). There is an ongoing debate around the possible adverse effects of n-3 LC-PUFAs on bleeding risk, particularly relevant in people with a medical history of cardiovascular events or using antithrombotic drugs.

Methods: This analysis of 8 clinical intervention studies conducted with enteral medical nutrition products containing fish oil as a source of n-3 LC-PUFAs addresses the occurrence of bleeding-related adverse events and effects on key coagulation parameters (Prothrombin Time [PT], (activated) and Partial Thromboplastin Time [(a)PTT]).

Results: In all the patients considered (over 600 subjects treated with the active product in total), with moderate to severe disease, with or without concomitant use of antithrombotic agents, at home or in an Intensive Care Unit (ICU), no evidence of increased risk of bleeding with use of n-3 LC-PUFAs was observed. Furthermore there were no statistically significant changes from baseline in measured coagulation parameters.

Conclusion: These findings further support the safe consumption of n-3 LC-PUFAs, even at short-term doses up to 10 g/day of eicosapentaenoic acid + docosahexaenoic acid (EPA + DHA) or consumed for up to 52 weeks above 1.5 g/day, in selected vulnerable and sensitive populations such as subjects with gastrointestinal cancer or patients in an ICU. We found no evidence to support any concern raised with regards to the application of n-3 LC-PUFAs and the potentially increased risk for the occurrence of adverse bleeding manifestations in these selected patient populations consuming fish oil enriched medical nutrition.

1. Introduction

Polyunsaturated fatty acids (PUFAs) are fatty acids which contain more than one double bond in their structure. The two main classes of PUFAs are the omega-6 (n-6) and omega-3 (n-3). N-

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3 PUFAs include α-linolenic acid (ALA; 18:3Δ9c,12c,15c or C18:3n-3), and 3 long-chain PUFAs (LC-PUFAs): eicosapentaenoic acid (EPA; 20:5Δ5c,8c,11c,14c,17c or C20:5n-3), docosapentaenoic acid (DPA; 22:5Δ7c,10c,13c,16c,19c or C22:5n-3) and docosahexaenoic acid (DHA; 22:6Δ4c,7c,10c,13c,16c,19c or C22:6n-3). The main dietary sources of EPA, DPA and DHA are fatty fish and fish oils produced either from fatty fish or from livers of lean fish. Other sources include human milk and oils from marine mammals, krill or marine algae. N-3 LC-PUFA enriched-foods such as milk, cheeses or spreads and food supplements are also available on the market. The body can convert ALA to EPA, DPA and DHA but this conversion rate, especially to DHA, is generally limited and inadequate to provide LC-PUFAs in sufficient amount to reach the recommended levels.

N-3 LC-PUFAs are involved in a variety of physiological processes, and their intake is associated with positive effects on cardiovascular health, brain function, immunity and inflammation [1,2].

These potential health benefits have led several expert committees to define recommended intakes in healthy populations. The EFSA panel on Dietetic Products, Nutrition and Allergies has proposed an Adequate Intake of 250 mg/day for EPA + DHA for healthy adults for the primary prevention of cardiovascular disease [3]. For people with cardiovascular disease or a medical history of cardiovascular disease, recommended n-3 LC-PUFA intakes are higher. For instance, the American Heart Association advises subjects with history of coronary heart disease to consume 1 g EPA + DHA per day from fish or supplements [4].

A consequence of an increased use of fish oil supplements is that a wide diversity of people, including elderly and those with impaired health will be exposed to n-3 LC-PUFAs in relatively high amounts. From the early observations in the Greenland Inuit population of a significantly longer bleeding-time associated with their very high n-3 LC-PUFA intakes [5], an ongoing debate exists around the possible adverse effects of n-3 LC-PUFAs on bleeding risk. This might be particularly relevant considering the specific recommendations to people with a medical history of cardiovascular events or patients in preparation for upper gastrointestinal surgery, who frequently use antithrombotic drugs (anticoagulant (AC) or platelet aggregation inhibitors (PAI) drugs) [6].

EPA and DHA are incorporated into cell membranes, where they shift the n-3/n-6 ratio of LC-PUFAs, partly replacing the n-6 LC-PUFA arachidonic acid (AA) which is the precursor for the synthesis of many eicosanoids, including prostaglandins, thromboxanes, and leukotrienes. At higher n-3 LC-PUFA concentrations, the competition with AA for cyclooxygenase enzymes leads to a reduction in synthesis of thromboxane A2, a potent promoter of platelet aggregation, and an increase in the formation of thromboxane A3 from EPA, which is a weak platelet aggregation factor [7]. N-3 LC-PUFAs are also suspected to have an impact on levels of some blood coagulation factors, but the results reported from different studies are not consistent. There are some reports that increased intake of n-3 LC-PUFAs leads to a decrease in blood levels of prothrombin, von Willebrand factor and factor V, and in an increase in protein C level in plasma [8,9]. These effects provide plausible mechanisms for reduced blood coagulation and could account for the observations in Inuits. These effects have also raised a concern about the potential effects of high n-3 LC-PUFA intake on blood coagulation in various patient groups.

In order to evaluate the safety of n-3 LC-PUFAs, we looked at the effect of n-3 LC-PUFA-enriched enteral medical nutrition products in patients included in Nutricia sponsored human intervention studies conducted after 2007. Blood coagulation parameters and bleeding-related adverse events were specifically assessed. Eight clinical studies with enteral products enriched in n-3 LC-PUFAs at or above 1.5 g EPA + DHA/day in persons with a variety of different diseases were evaluated.

2. Materials and methods

Six published and one unpublished randomized (registration number NTR1966), double-blind, controlled clinical studies involving n-3 LC-PUFA enriched enteral medical nutrition products performed by Nutricia Research between March 2007 and February 2013 were reviewed specifically for effects on coagulation parameters and (bleeding-related) adverse effects [10–15]. An open label extension (OLE) study in which all subjects received a n-3 LC-PUFA-enriched product was also reviewed [16]. The majority of studies took place in Europe (Netherlands, Germany, Spain, France, Belgium, Spain, Italy and UK), one study was solely conducted in the US, and one study also had recruitment centres in Argentina, Australia, Brazil and Thailand. All protocols had originally been reviewed and approved by the local ethical committees and the studies fully conformed with the principles of the "Declaration of Helsinki" (52nd WMA General Assembly, Edinburgh, Scotland, October 2000), Good Clinical Practice guidelines and with local legislation of the country in which the research was conducted.

2.1. Study populations

Three studies were conducted in oncology patients. One study was carried out in subjects with newly diagnosed oesophageal cancer [11], and the other two included patients with a variety of tumour types and locations, not under treatment during the study period, with the majority including lower gastrointestinal or breast cancers [10,11]. The remaining studies included one performed in human immunodeficiency virus-1 (HIV-1) infected patients not on antiretroviral therapy [12], one in mechanically ventilated patients in intensive care units (ICUs) [15], and three in patients with Alzheimer's disease (AD). Two of the latter trials were in drug naïve, mild AD subjects [14,16], and the other one included subjects with more advanced disease on AD medication [13].

Except in NUSPEC and BITE studies, the consumption of any other food supplements containing vitamins, minerals and/or omega-3 fatty acids or fish oil was not allowed by the subjects. In the 2 other studies, it was not forbidden but was not recommended either and strictly monitored.

All subjects included in the 8 clinical trials were adults and gave their informed written consent, or this was obtained from their representative in the case of the patients in an ICU. Detailed inclusion or exclusion criteria can be found in the scientific publications of the studies.

2.2. Study products

Three studies investigated the effects of an energy dense protein-rich nutritionally complete oral nutritional supplement designed for patients with cancer [10,11]. Three other studies were performed with Souvenaid® (Nutricia NV, Zoetermeer, The Netherlands), an oral product for the dietary management of early AD, currently available on the market [13,14,16], and one with a nutritional concept consisting of a special blend of fibres, proteins and fats [12]. In the study from van Zanten et al. [15], performed in critically ill ICU patients, a high-protein tube feed, enriched with immune-modulating nutrients was used.

Levels of n-3 LC-PUFAs administered orally ranged from 1.5 to 3.6 g/day. In the tube feeding study, target energy intake was 25 kcal/kg body weight/day. For a 70-kg adult, this corresponded to 6.8 g/day EPA + DHA. Feeding was introduced gradually towards this target. The minimal mean intake of 1.5 g EPA + DHA (+/−1.2 g) was reported at day 1 whereas the highest mean intake of 5.6 g/day (+/−2.8 g) was reported at day 9. In practice for some subjects, the maximum EPA + DHA intake was 10.2 g/day. In all studies where

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