ORIGINAL RESEARCH

Effect of Omega-3 Fatty Acids on Serum Lipid Profile and Oxidative Stress in Pediatric Patients on Regular Hemodialysis: A Randomized Placebo-Controlled Study

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Objective: We sought to evaluate the effects of omega-3 fatty acids supplementation on serum lipid profile and oxidative stress markers in pediatric patients with end-stage renal disease on regular hemodialysis (HD).

Design: This study was a double-blinded, randomized, placebo-controlled trial conducted on 49 pediatric patients on regular HD for at least 6 months.

Intervention: Patients were randomly divided into either omega-3 group (n = 25) who received 1-g oral omega-3 capsule once daily for 16 weeks or placebo group (n = 24) who received 1-g matching oral placebo capsule once daily for 16 weeks.

Main Outcome Measure: Lipid profile markers including: total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and oxidative stress markers including the following: malondialdehyde, glutathione peroxidase, and superoxide dismutase were measured at baseline and after 16 weeks of supplementation.

Results: By the end of the study, children in omega-3 group showed a highly significant reduction in total cholesterol and a highly significant increase in glutathione peroxidase and superoxide dismutase levels.

Conclusion: The administration of omega-3 has a beneficial effect on serum lipid profile and oxidative stress in children undergoing HD.

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Introduction

CARDIOVASCULAR DISEASE (CVD) is the leading cause of death in children with end-stage renal disease (ESRD), with risk 1,000 times higher when compared to the age-matched non-ESRD population.[1] Several risk factors contribute to CVD in these patients.[2] Traditional risk factors include hypertension, dyslipidemia, hyperglycemia, and obesity.[3] Dyslipidemia is an important cardiovascular risk factor in the general population.[4] In patients with ESRD, dyslipidemia is characterized by increased triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C) levels and reduced levels of high-density lipoprotein cholesterol (HDL-C).[3] These lipid abnormalities persist and are aggravated during hemodialysis (HD)[5,6] which may partly explain the high incidence of CVD in these patients.[7] However, traditional risk factors alone cannot completely explain the high CVD risk in ESRD population.[8] Recently, nontraditional risk factors such as oxidative stress have attracted more interest for the occurrence of CVD events in ESRD patients.[9] Oxidative stress is defined as the tissue damage resulting from an imbalance between an excessive generation of oxidant compounds and insufficient antioxidant defense mechanisms.[10] Antioxidant mechanisms can be divided into intracellular and extracellular antioxidants. Intracellular antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase (GP), which convert substrates (superoxide anion radicals and hydrogen peroxide) into less reactive forms.[11] Factors such as exposure of the blood to dialysis membranes, high risk of acute and chronic infection, and dietary limitations in the intake of antioxidant nutrients make patients on HD susceptible to more oxidative stress.[12] In chronic kidney disease, oxidative stress is characterized by increased concentrations of malondialdehyde (MDA) as a marker of lipid peroxidation and reduced concentrations of SOD and GP as markers of antioxidants.[11]

Omega-3 fatty acids are polyunsaturated fatty acids that are mainly obtained from dietary sources especially fatty

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Financial Disclosure: The authors declare that they have no relevant financial interests. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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1051-2276/$36.00

http://dx.doi.org/10.1053/j.jrn.2016.11.005

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fish.[13] There is strong evidence from clinical trials that omega-3 fatty acids significantly decrease cardiovascular mortality, improve the lipid status, and have antioxidant effects.[14] ESRD patients are at risk for inadequate omega-3 intake because dialysis patients may find foodstuffs less palatable as a result of uremia-associated alterations in taste and renal dietary recommendations that do not encourage fish consumption.[15] On the basis of the above data, it was suggested that omega-3 intake may offer a host of benefits to the pediatric patients with ESRD. Thus, the aim of the study was to evaluate the effects of oral omega-3 intake on serum lipid profile, oxidative stress, and antioxidant markers in pediatric patients on regular HD.

Methods

Study Design and Population

This study was a prospective, randomized, double-blinded, placebo-controlled study. It was conducted on pediatric patients with ESRD who were undergoing HD from March 2015 to September 2015.

Inclusion and Exclusion Criteria

Patients between 8 and 18 years old who have been on regular HD for >6 months were included in the study. Patients with malignancy and/or active inflammatory disease and those who received vitamin E during the past 3 months were excluded from the study. The HD regimen of all patients typically consisted of HD sessions of 3-4 hours, 3 days per week.

Sample Size Calculation

Sample size was calculated according to the oxidative stress marker MDA. Based on a previous study conducted on patients undergoing HD,[12] a difference of 0.9 nmol/L was found between groups with a standard deviation (SD) = 0.9 and 0.7 in the treatment group and the control group, respectively. With this information, we obtained a sample size of 22 patients per group for a 90% statistical power with $\alpha = 0.05$. All patients in the dialysis unit who fulfilled the inclusion and exclusion criteria (n = 53) were included in the study. Only 49 patients completed the study. Three patients were dropped out due to noncompliance, and 1 patient underwent renal transplantation.

Randomization

The patients were randomly assigned into either omega-3 group (n = 25) or placebo group (n = 24).

Intervention

Patients in omega-3 group received 1-g oral omega-3 capsule once daily for 16 weeks. Patients in placebo group received 1-g oral placebo capsule once daily for 16 weeks. Omega-3 capsules were supplied by NOW FOODS company, USA, under the trade name of Ultra Omega-3®, containing 500 mg eicosapentaenoic acid and 250 mg docosahexaenoic acid in addition to the standard ingredients of soft gelatin capsules. Placebo capsules contain only the standard ingredients of soft gelatin capsules (gelatin, water, glycerin, and vitamin E in minute amounts as preservative). Placebo capsules were carefully matched in size, shape, and color with the omega-3 capsules. The dose of omega-3 was given based on the Council on Food and Nutrition of the American Medical Association published in 2002.[16]

Patients were monitored weekly for any adverse effects of omega-3 fatty acids. Weight was measured after the HD session with subjects bare feet and wearing light clothes. Height was measured using a nonstretchable tape with subjects standing bare feet with heels touching the floor and eyes directed straight ahead. Weight and height z scores were calculated using Centers for Disease Control and Prevention growth charts as recommended by the World Health Organization.

Assays

Blood samples were drawn from the patients at baseline and after 16 weeks of supplementation. Blood samples were collected before the dialysis session after 12 hours overnight fasting. Total cholesterol (TC), TG, HDL-C, LDL-C, and GP were assayed by spectrophotometric method using commercial kit manufactured by Biodiagnostic Company, Giza, Egypt. The GP activity was measured indirectly through a coupled reaction with glutathione reductase. Oxidized glutathione produced upon reduction of an organic hydroperoxide by GP was recycled to its reduced state by glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH). The oxidation of NADPH to oxidized form of NADPH ($NADP^+$) is accompanied by a decrease in absorbance at 340 nm. Enzyme-linked immunosorbent assay method was used to measure MDA and SOD concentrations. A commercial kit OxiSelect™ MDA Adduct manufactured by Cell Biolabs Inc., USA, was used for MDA assay, while a commercial kit manufactured by Northwest Life Science Specialties, LLC, USA, was used for SOD assay.

An informed consent was obtained from either parents or children aged >16 years. The Ethics Committee of the Faculty of Pharmacy, Ain Shams University, approved the study protocol. The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Data management and analysis were performed using Statistical Package for Social Sciences versus 21. Numerical data were summarized using means and SDs or medians and interquartile ranges, as appropriate. Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using Kolmogrov–Smirnov test and Shapiro–Wilk test. Exploration of data revealed that the collected values were not normally distributed. Comparisons between the 2 groups with respect to numerical variables were done by Mann–Whitney test. Change overtime for each group was tested using Wilcoxon Rank Signed test. These tests were followed by the post hoc

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