INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Eicosapentaenoic Acid (EPA) Decreases the All-Cause Mortality in Hemodialysis Patients

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Abstract

Objective Atherosclerosis, which causes cardiovascular disease, is a major cause of death in hemodialysis (HD) patients. Eicosapentaenoic acid (EPA), an anti-hyperlipidemic agent, is known to have antioxidative or anti-inflammatory effects, resulting in improvements in atherosclerosis. In the present study, we examined whether EPA improves the all-cause mortality in patients receiving regular HD therapy.

Methods We enrolled 176 patients treated with maintenance HD therapy and performed a longitudinal observational cohort study for three years. We divided the patients into two groups based on whether or not the received EPA treatment [EPA(+) and EPA(-), respectively]. The primary end-point was all-cause death. We also matched the two groups using propensity score matching and examined the effect of EPA.

Results Before matching, the all-cause mortality rates were 24.0% in the EPA(+) and 11.8% in the EPA(-) groups, which were significantly different (p=0.044). After propensity score matching, the EPA(+) group still showed a significantly better prognosis than the EPA(-) group (p=0.038). A multivariate analysis showed that EPA treatment significantly reduced the risk of all-cause mortality both before and after propensity score matching.

Conclusion EPA treatment is independently associated with lower mortality in HD patients.

Key words: dialysis, eicosapentaenoic acid, fish oil, mortality

(Intern Med 54: 3133-3137, 2015)
(DOI: 10.2169/internalmedicine.54.4931)

Introduction

Cardiovascular disease (CVD) remains one of leading causes of mortality in patients with end-stage renal disease (1). Although traditional risk factors, such as old age, smoking, hypertension, and diabetes mellitus, are fairly common in maintenance hemodialysis (HD) patients, hyperlipidemia is less common in the population (2). The cause(s) of atherosclerosis in HD patients are complicated, but the accumulation of atherogenic lipoproteins in the plasma could be one of the risk factors (3). Further, oxidative stress is elevated in the HD population compared with healthy controls, which may contribute to the high levels of CVD mortality (4). It is possible that remnant lipoproteins and oxidized low-density lipoprotein (LDL) play a key role in the acceleration of atherosclerosis (5). An imbalance in oxidative stress and the generation of reactive oxygen species (ROS) can be caused by several factors, such as a loss of antioxidants by HD, or interaction with the dialysis membrane (6).

Polyunsaturated fatty acids (PUFA) of fish oil origin, especially eicosapentaenoic acid (EPA), have been used to treat or prevent hyperlipidemia. Further, EPA has been reported to have several protective roles, such as attenuating lipid metabolism, lowering blood pressure, improving the vascular endothelial function, reducing neutrophil and monocyte cytokine production and inhibiting thrombogenesis and the inflammatory response (7-10). EPA also upregulates the expression of antioxidant enzymes, downregulates genes associated with the production of ROS, and suppresses the production of oxidative stress by decreasing the production

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Received for publication January 14, 2015; Accepted for publication June 16, 2015
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of pro-inflammatory cytokines (11, 12). The inhibitory role of EPA on the progression of atherosclerosis may be beneficial for decreasing the morbidity due to CVD in the HD population. Ando et al. reported that oral administration of EPA effectively reduced both the plasma remnant lipoproteins and oxidative LDL levels in HD patients (5). However, the potential benefits of administering EPA to the HD population remain unclear. One reason may be that EPA is not administered to many HD patients, because most of them do not show hyperlipidemia. In the present study, we evaluated whether EPA has a beneficial effect on the all-cause mortality in patients receiving regular HD therapy.

Materials and Methods

This was a longitudinal observational cohort study conducted over a period of three years from January of 2008 to December of 2011 (mean follow up, 36.9±9.2 months). We enrolled 176 patients treated with maintenance HD therapy (HD duration >3 months) at Tokyo Women's Medical University Hospital (Tokyo, Japan) and Tsuruta Clinic (Tokyo, Japan). All of the patients provided written informed consent before their enrollment in the study. Of these patients, those undergoing combination treatment comprising HD and peritoneal dialysis or immunosuppressive therapy, those with significant infections or clinically apparent malignancy, and patients younger than 20 or older than 85 years old were excluded. We also excluded the patients who underwent renal transplantation or moved to other dialysis centers for any reason.

We divided the patients into two groups based on whether they received EPA treatment [EPA(+) and EPA(-) groups]. Basically, the EPA prescription was started for most patients to treat mild hyperlipidemia, but for some patients, it was prescribed due to the high viscosity of circulating blood. The dose of EPA was 1,800 mg daily. The amount of EPA was reduced to 600 mg or 1,200 mg daily in three patients in the EPA(+) group, but none of the patients stopped taking EPA during the observation period. The patients in the EPA(-) group did not have an EPA prescription during the follow-up period.

The causes of uremia in the HD patients were chronic glomerulonephritis (n=101), diabetes mellitus (n=29), nephrosclerosis (n=7), polycystic kidney disease (n=13) and other diseases, including diseases with unknown causes (n=26). The patients underwent stable maintenance HD three times a week. HD was performed with single-use hollow-fiber dialyzers equipped with modified cellulose-based or polysulfone membranes at a blood flow rate of 150-300 mL/min and a dialysate flow rate of 500 mL/min. The dialysate solution contained Na^+ (140 mmol/L), K^+ (2.0 mmol/L), Ca^{2+} (1.5 mmol/L) and HCO_3^- (30 mmol/L). Regular heparin was used for the treatment.

The primary endpoint of the study was all-cause death. The clinical profiles and analytical data for the patients were collected from hospital records. Blood samples for hematological and biochemical analyses were collected after at least 10 hours of fasting, just before the first HD session of the week, and were tested in the laboratory at SRL (Tokyo, Japan). A paired *t*-test or the Mann-Whitney *U*-test was used to compare parametric or non-parametric data from the hematological and biochemical analyses, respectively. The Chi-square test was used to compare categorical data such as the sex ratio, primary disease, complications, etc. The survival rate was analyzed using Kaplan-Meier curves and the log-rank test. Hazard ratios (HRs) for all-cause mortality were determined using a multivariate Cox proportional hazards regression analysis.

In order to assemble a cohort of patients for comparisons between groups, propensity score matching was performed. The following covariates were used to match the patients: age, gender, dialysis vintage, diabetes mellitus status, and the hemoglobin, albumin, Ca, P, ferritin, and C-reactive protein levels. Matching was performed using a 1:1 matching protocol without replacement (Greedy matching algorithm) with a caliper width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. The data in the text, tables, and figures are basically expressed as the means ± SD. A value of $p < 0.05$ was considered to be statistically significant. All analyses were performed using the JMP 11.2.0 software program (SAS Institute, Cary, USA).

Results

Table 1 shows the characteristics of the participants in the EPA(+) and EPA(-) groups. The baseline characteristics of matched patients (n=49 in each group) are also shown in Table 1. After matching, there were no significant differences in the clinical data, primary disease, complications, or medications between the two groups, except for the use of antiplatelet agents. The laboratory data at the start of the observational period are shown in Table 2. Except for the serum ferritin levels, there were no significant differences in any of the hematological or biochemical factors between the two groups. There was also no significant difference observed in the serum triglyceride or total cholesterol level between the two groups. Before matching, 30 (24%) and six (11.8%) of the patients in the EPA(+) and EPA(-) groups (respectively) had died. After matching, six (12.2%) patients in the EPA(+) group and 13 (26.5%) patients in the EPA(-) group had dead. Table 1 shows the numbers of cardiovascular-, cerebrovascular-, and other deaths in each group. There was a significant difference in the all-cause mortality between the two groups both before and after matching (Figure).

Next, we performed a multivariate analysis that included several important prognostic factors, such as age, the presence of diabetes mellitus, serum hemoglobin levels, serum albumin levels, serum calcium levels, serum phosphate levels, serum ferritin levels, and the serum C-reactive protein levels. After adjustment, the EPA(+) group still showed a significant reduction of the HR for all-cause mortality compared to the EPA(-) group both before and after matching

Table 1. The Basal Characteristics of the Hemodialysis Patients with and without Eicosapentaenoic Acid (EPA) Supplementation.

	Pre-Matching			Post-Matching		
	EPA(-) (n = 125)	EPA(+) (n = 51)	p	EPA(-) (n = 49)	EPA(+) (n = 49)	p
Male : female	74 : 51	32 : 19	0.662	22 : 27	24 : 25	0.685
Age (years old)	59.9 ± 14.7	62.4 ± 14.7	0.890	58.5 ± 15.8	59.2 ± 13.3	0.798
Cases with hypertension (%)	79 (63.2)	28 (54.9)	0.306	30 (61.2)	24 (49.0)	0.223
Primary disease						
CGN	74	27	0.446	24	27	0.544
Nephrosclerosis	5	2	0.981	4	2	0.399
ADPKD	9	4	0.882	3	4	0.695
DM	15	14	0.012	10	12	0.628
Others	22	4	0.098	8	4	0.218
Complication						
Cardiovascular	29	16	0.260	13	14	0.821
Cerebrovascular	15	9	0.322	7	9	0.585
PAD	20	6	0.473	13	6	0.074
Medication						
ACEI/ARB	44	16	0.627	18	13	0.277
CCB	41	15	0.662	18	15	0.521
α-blocker	4	0	0.196	3	0	0.076
β-blocker	14	5	0.187	12	5	0.062
Anticoagulant	8	6	0.233	3	6	0.294
Anti-platelet	51	30	0.074	16	28	0.015
Statins	8	6	0.233	4	3	0.695
Anti-hyperlipidemia	16	11	0.143	5	11	0.101
Cause of death						
Total	30	6	0.068	13	6	0.074
Cardiovascular	9	2	0.415	5	2	0.239
Cerebrovascular	3	1	0.859	2	1	0.558
Others	18	3	0.179	6	3	0.294

The data are expressed as the means ± SD, except for the number of patients and the patient sex. CGN: chronic glomerulonephritis, ADPKD: autosomal dominant polycystic kidney disease, DM: diabetes mellitus nephropathy, PAD: peripheral arterial disease, ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, CCB: calcium channel blocker

(Table 3). These findings indicate that EPA administration was independently associated with lower mortality in HD patients.

Discussion

In the present study, we investigated the effects of EPA on the all-cause mortality of HD patients. There were several previous reports that described the beneficial effects of PUFA on the mortality from CVD in non-HD populations (13, 14). Intervention trials also demonstrated the preventative effects of PUFA on CVD events (15). Despite the high incidence of CVD, the severity of hyperlipidemia is generally mild in HD population, resulting in a low frequency of administration of anti-hyperlipidemic agents. Kunter et al. reported that fish oil did not lead to a significant reduction in the CVD deaths in HD patients (16). In another study, PUFA supplementation significantly reduced the incidence of myocardial infarction in HD patients (17). A new finding of the present study is that EPA treatment was associated with reduced mortality in the HD population, even when there was no significant differences in the serum lipid levels between the EPA(+) and the EPA(-) groups.

Several mechanisms may contribute to the beneficial effects of EPA for reducing the all-cause mortality in HD patients. In an *in vivo* study, EPA reduced the severity of warfarin-induced arterial medial calcification in rats (18). EPA reduces the serum remnant lipoprotein and oxidative LDL in HD patients, suggesting that it has an antioxidative role (5). EPA attenuates the infiltration and activation of inflammatory cells in atherosclerotic lesions (19).

EPA and docosahexaenoic acid (DHA) are two different types of PUFA. Hamazaki reported that HD patients with higher levels of DHA in their red blood cells showed a better prognosis than those with lower levels (20). It remains to be determined which of the PUFAs is more effective for reducing mortality in HD patients. However, it is likely that not only the anti-hyperlipidemic effects, but also the antioxidative and anti-inflammatory effects of PUFAs have a beneficial impact on the mortality of HD patients.

The administration of EPA has some advantages compared to other agents, such as fibrates or statins. Fibrates strongly reduce the serum triglyceride-rich lipoprotein levels because they stimulate the catabolism of VLDL (21). However, using these agents for HD patients is not recommended because of the various adverse effects associated with their

Table 2. The Laboratory Data of the Participants at Entry into the Study.

	Pre-Matching			Post-Matching		
	EPA(-) (n = 125)	**EPA(+)** (n = 51)	p	**EPA(-)** (n = 49)	**EPA(+)** (n = 49)	p
WBC (/mm^3)	5,539±152	5,835±238	0.318	5,809±1,646	5,872±2,024	0.867
Hb (g/dL)	10.8±1.3	10.6±1.2	0.488	10.4±1.4	10.7±1.2	0.254
Alb (g/dL)	3.9±0.4	3.8±0.4	0.266	3.9±0.4	3.8±0.3	0.865
Cr (mg/dL)	11.34±2.87	11.09±3.14	0.565	10.67±2.79	11.25±3.08	0.333
UA (mg/dL)	7.3±0.1	7.2±0.2	0.591	7.3±1.3	7.2±1.3	0.330
Na (mEq/L)	138.8±0.2	139.2±0.0	0.350	138.3±3.2	139.3±3.0	0.118
K (mEq/L)	5.1±0.1	4.8±0.1	0.071	4.9±0.7	4.9±0.7	0.564
Ca (mg/dL)	9.1±0.1	8.8±0.1	0.145	8.8±0.6	8.9±0.7	0.731
P (mg/dL)	5.3±1.3	5.2±1.3	0.657	5.1±1.2	5.2±1.3	0.665
spKt/V	1.62±0.56	1.94±0.73	0.604	1.49±0.59	1.72±0.64	0.473
CRP (mg/dL)	0.51±1.10	0.43±0.91	0.827	0.60±1.01	0.52±1.12	0.422
HbA1C (%)	6.3±0.7	6.3±1.2	0.964	6.4±0.8	6.0±0.9	0.231
Ferritin (ng/mL)	126.5±29.6	303.9±47.1	0.001	146.3±221.3	314.1±464.2	0.026
TG (mg/dL)	103.1±55.5	100.1±4.9	0.711	109.6±70.5	109.51±28.9	0.819
TC (mg/dL)	157.2±37.5	157.1±37.3	0.918	161.6±39.3	155.9±37.5	0.467
β2MG (mg/L)	27.1±0.6	28.2±0.9	0.309	27.7±7.4	28.6±6.0	0.490
wPTH (pg/mL)	154.2±14.5	127.9±22.5	0.338	145.1±183.6	130.8±133.3	0.660

The data are expressed as the means ± SD. WBC: white blood cell, Hb: hemoglobin, Alb: serum albumin, Cr: serum creatinine, UA: serum uric acid, Na: serum sodium, K: serum potasium, Ca: serum calcium, P: serum phosphorus, spKt/V: single pooled Kt/V, HbA1C: hemoglobin A1C, TG: serum total triglycerides, TC: serum total cholesterol, β2MG: beta2-microglobulin, wPTH: serum whole parathyroid hormone

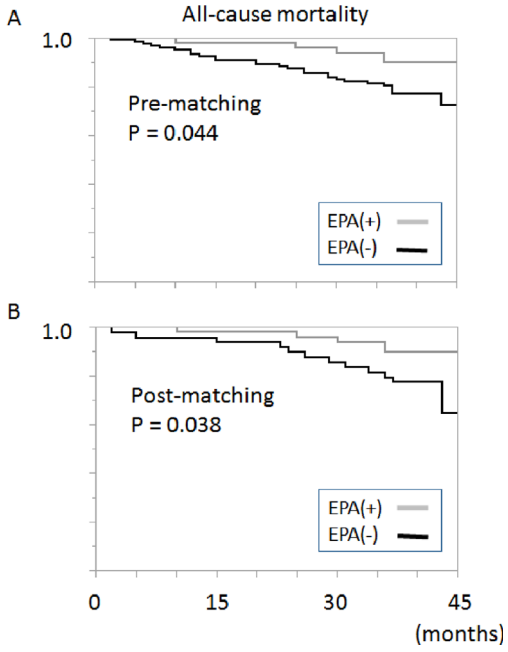

Figure. The Kaplan-Meier estimates of the all-cause mortality at 45 months for HD patients with or without eicosapentaenoic acid (EPA) treatment. (A) The patients were divided into two groups based on their EPA use. No propensity score matching was performed (pre-matching). (B) The patients in the two groups were matched using propensity score matching and the all-cause mortality was examined (post-matching).

use (22). Statins have been shown to decrease the mortality and CVD events in people with early stages of CKD, but have little or no effect on the HD population, and have uncertain effects in kidney transplant recipients (23). The detailed relationships among the plasma cholesterol level, cholesterol reduction, the use of statins, and the reduction of CVD have not been proven in the HD population (24). Thus, although fibrates and statins are not indicated for HD patients without hyperlipidemia, EPA or DHA supplementation may be suitable for treating milder disorders of lipid metabolism because of their rare induction of adverse reactions.

Despite the novel findings, the present study suffers from several limitations. First, there was a wide range of pre-study HD history and EPA administration prior to the study, although the duration of pre-study HD was adjusted as a covariate. Second, the number of patients who died in each disease category was not sufficiently large to separately calculate the effects of EPA. Third, the present study included only two HD centers, so the results may not translate to other centers. For example, Japanese subjects have a higher dietary intake of fish compared to those in the USA and northern Europe (25), and this may have affected the findings.

In conclusion, EPA treatment is independently associated with lower mortality in HD patients. Further studies, such as a large clinical trial, will be needed to determine whether

Table 3. The Results of the Multivariate Cox Analysis for All-Cause Mortality.

		HR	95%CI	p
pre-matching	**model 1 (single)**	0.417	0.156 - 0.939	0.034
	model 2 (age + DM)	0.377	0.139 - 0.864	0.020
	model 3 (model 2 + Hb + Alb + CRP)	0.330	0.121 - 0.764	0.008
	model 4 (model 3 + Ca + P + Ferritin)	0.235	0.080 - 0.582	0.001
post-matching	**model 1 (single)**	0.370	0.129 - 0.947	0.038
	model 2 (age + DM)	0.376	0.131 - 0.958	0.040
	model 3 (model 2 + Hb + Alb + CRP)	0.375	0.128 - 0.981	0.045
	model 4 (model 3 + Ca + P + Ferritin)	0.293	0.092 - 0.810	0.017

HR: hazard ratio, 95%CI: 95% confidence interval, DM: diabetes mellitus, Hb: hemoglobin, Alb: albumin, Ca: calcium, P: phosphorus, CRP: C-reactive protein

HD patients should receive EPA treatment to obtain a better prognosis.

The authors state that they have no Conflict of Interest (COI).

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