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DOES ADDITIONAL TREATMENT WITH FISH OIL MITIGATE THE SIDE EFFECTS OF RECOMBINANT HUMAN ERYTHROPOIETIN IN DIALYSIS PATIENTS?

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ABSTRACT

Since fish oil has been reported to reduce platelet aggregability, to reduce blood viscosity by increasing red blood cell deformability and to lower blood pressure, we studied the effect of dietary supplementation with fish oil on the occurrence of adverse effects in patients receiving recombinant human erythropoietin (rHuEPO). In a prospective, randomized, double blind cross-over design we studied the effect of daily ingestion of 3 g fish oil versus 3 g corn oil (placebo) for 5 months, with a wash-out period of 3 months in between. Thirty-two dialysis patients newly treated with rHuEPO participated. rHuEP0 was given using a *low and slow* dose regimen (25 U/kg twice weekly s.c.). Target Hct was 35%. Blood pressure, red blood cell deformability, plasma viscosity, fatty acid composition of plasma phospholipids, and fibrinogen levels were measured at 0, 5, 8 and 13 months. In both groups a stable target Hct (35%) was reached within 3 months. Blood pressure was not significantly different between the groups at any time point. In 4 patients (2 on fish oil and 2 on placebo) antihypertensives had to be increased to regulate blood pressure adequately, whereas shunt occlusion occurred in one patient on placebo. Despite a significant increase in the ω-3 fatty acid content of plasma phospholipids during ingestion of fish oil, no significant changes in red blood cell deformability were observed. Since hypertension and shunt occlusion occurred at rates comparable to those reported in the literature, long-term ingestion of fish oil does not appear to mitigate the side effects of *low and slow* dose rHuEPO.

Key words: fish oil, erythropoietin, hypertension, thrombogenicity, dialysis

The efficacy of recombinant human erythropoietin (rHuEPO) in correcting anemia in dialysis patients has been demonstrated in several studies.[1,2] However, hypertension and thrombosis at the site of vascular access have been the two main side effects reported within these trials.[3]

Since fish oil has been observed to reduce platelet aggregability, to reduce blood viscosity by increasing red blood cell deformability and to lower blood pressure,[4-7] we studied the effect of dietary supplementation with fish oil versus placebo (corn oil) on the occurrence of these adverse effects in patients newly treated with rHuEPO in a prospective, randomized, double blind cross-over study.

Patients and Methods

Thirty-two dialysis patients started on rHuEPO using a *low and slow* dose administration regimen (25 U/kg twice weekly subcutaneously), adjusted monthly in order to achieve (within three months) and maintain a stable target hematocrit of 35%. The first five months of rHuEPO therapy were accompanied by daily oral ingestion of either 6 corn oil capsules (placebo; EPA-A) or 6 fish oil capsules (EPA-B), kindly provided by Pharmacaps Inc., Marlow, Buckinghamshire, UK. Each fish oil capsule provided 1.0 g of fat, 500 mg of which were composed of fatty acids EPA-C 20:5 ω-3 and DHA-C 22:6 ω-3 as their methylesters, and 1 IU of vitamin E.[8]

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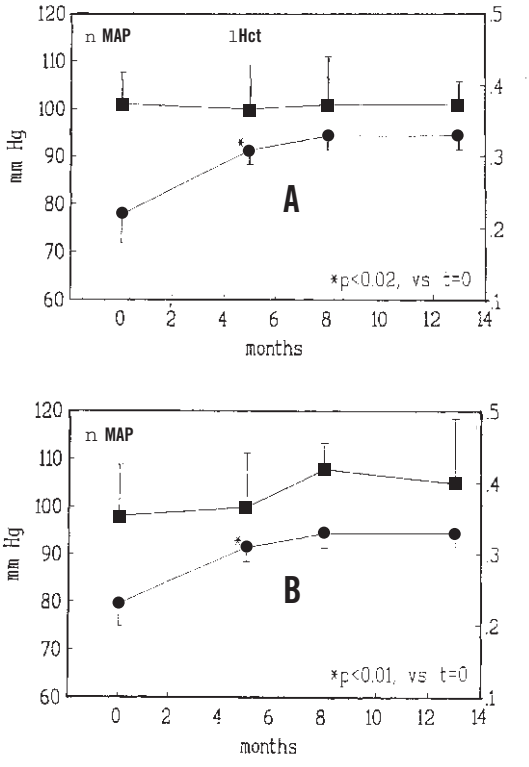

Figure 1. Blood pressure and hematocrit levels of patients treated with rHuEPO and daily supplementation of EPA-A (placebo=corn oil) and EPA-B (fish oil). **A.** Patients starting with EPA-A (5 months), followed by a *wash-out* of 3 months and subsequently EPA-B for 5 months. **B.** Patients starting with EPA-B and following the reverse procedure.

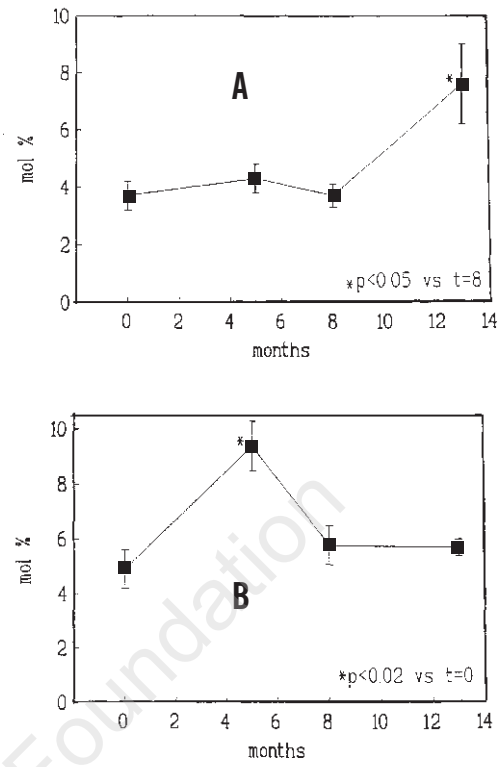

Figure 2. Plasma phospholipid content of omega-3 fatty acids (in mol%) in patients treated with rHuEPO and daily supplementation of EPA-A (placebo=corn oil) or EPA-B (fish oil) in a double-blind cross-over design. For A and B see Figure 1.

Following a three-month wash-out period, patients switched study arms regarding the dietary supplementation, whereas rHuEPO administration was continued throughout the study.

All patients were studied for the following parameters: hemoglobin, hematocrit, blood pressure, thrombogenic events, red cell deformability (assessed by determining the viscosity of erythrocyte suspensions at a hematocrit of 0.80 using a Contraves Low Shear 30 Rheometer at shear rates varying from 0.081 to 94.5 per sec as described previously),[6] plasma viscosity, determined with the same Rheometer at a shear rate of 50 per sec, and serum fibrinogen levels. Measurements of these variables were performed at least at 0 (baseline), 5 (end of EPA-A or EPA-B supplementation), 8 (wash-out) and 13 months (end of EPA-B or EPA-A supplementation).

At these time points the fatty acid composition of plasma phospholipids was assessed as described previously[7] to control patient compliance regarding the intake of fish oil.

Results

Due to renal transplantation or change of dialysis unit (n = 10) and noncompliance (n = 6; no change in the fatty acid composition of plasma phospholipids during their EPA-B period), only 16 of the 32 patients newly treated with rHuEPO were evaluable. In both groups a stable target Hct (35%) was reached and maintained at the target level thereafter (Figure 1). Mean arterial blood pressure was not significantly different between the groups at any time point (Figure 1). In 4 patients (2 on fish oil and 2 on placebo) antihypertensives had to be increased to regulate blood pressure adequately,

Table 1. Effect of fish oil and placebo (corn oil) supplementation on plasma viscosity (mPascal x s) and viscosity of erythrocyte suspensions at Hct = 0.80 and various shear rates.

	fish oil-placebo			
	baseline	*fish oil*	*wash-out*	*placebo*
plasma viscosity				
	1.52±0.11	1.57±0.16	1.58±0.15	1.52±0.09
viscosity of erythrocytes (shear rate/sec)				
94.5	13.3± 0.8	13.0± 0.9	13.1±0.8	12.9± 0.99
51.2	15.0± 0.9	14.7± 0.9	14.8±0.9	14.6± 1.1
20.4	18.4± 1.1	18.0± 1.2	18.2±1.0	18.1± 1.3
8.11	24.1± 1.5	23.9± 1.5	24.0±1.3	23.9± 1.7
0.945	54.0± 4.9	53.2± 2.5	52.7±2.5	53.4± 4.4
0.081	213.9±28.1	210.9±19.3	208.3±9.8	210.8±21.9

	placebo-fish oil			
	baseline	*placebo*	*wash-out*	*fish oil*
plasma viscosity	1.49±0.10	1.54±0.13	1.52±0.08	1.50±0.06
viscosity of erythrocytes (shear rate/sec)				
94.5	13.7± 0.8	13.1± 0.4	13.0± 0.7	12.7± 0.5
51.2	15.4± 0.9	14.8± 0.5	14.6± 0.8	14.3± 0.6
20.4	18.9± 1.0	18.2± 0.6	17.9± 0.9	17.5± 0.7
8.11	25.7± 1.0	24.0± 1.0	23.6± 1.1	23.0± 0.8
0.945	56.6± 4.0	54.5± 3.8	53.2± 3.5	52.1± 1.8
0.081	226.6±22.5	214.3±22.4	209.2±21.1	203.4± 8.3

whereas shunt occlusion occurred in one of the 7 hemodialysis patients (on placebo at 11 months). Despite a significant increase in the ω-3 fatty acid content of plasma phospholipids (Figure 2) in all compliant patients during ingestion of fish oil, no significant changes in red blood cell deformability were observed (Table 1). Plasma viscosity and the (elevated) blood fibrinogen levels remained unchanged.

Discussion

In the present study the incidence of hypertension (4/16) and shunt occlusion (1/7 hemodialysis patients) during rHuEPO therapy was roughly in agreement with data reported in other studies using *low and slow* dose rHuEPO.[9,10] The slow increase in hematocrit with only partial correction of anemia during treatment with rHuEPO may allow time for hemodynamic adaptations to occur and for appropriate control of blood pressure, despite increasing blood viscosity.

Five months of daily addition of fish oil to the diet of dialysis patients did not confirm the results of a previous study, in which a decreased viscosity of erythrocyte suspensions was observed following short-term fish oil supplementation in patients on continuous ambulatory peritoneal dialysis.[5] However, in the present study red blood cell deformability was measured during a steady state (stable hematocrit and mean corpuscular volume) after 5 months of rHuEPO treatment. The observed absence of any effect of long-term ingestion of fish oil on red blood cell deformability is remarkable and remains to be explained.

In conclusion, long-term ingestion of fish oil does not appear to mitigate the side effects of rHuEPO when a *low and slow* dose regimen is applied.

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