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A Vitamin E-Coated Polysulfone Membrane Reduces Serum Levels of Inflammatory Markers and Resistance to Erythropoietin-Stimulating Agents in Hemodialysis Patients: Results of a Randomized Cross-Over Multicenter Trial

Vincenzo Panichi[a] Alberto Rosati[b] Sabrina Paoletti[a] Paolo Ferrandello[a] Massimiliano Migliori[a] Sara Beati[a] Giada Bernabini[a] Roberto Daini[c] Aldo Casani[c] Daniela Angelini[b] Manuela Parrini[b] Arturo Rossi[d] Isabella Petrone[d] Giuliano Barsotti[e] Carlo Donadio[e] Giaclì Donati[f] Giovanni Grazi[f] Giovanni Manca Rizza[f] Guido Garosi[g] Enrico Sansoni[g] Beatrice Braccagni[g] Antonino Sidoti[h] Donella Boracelli[h] Marina Biagioli[h] Luigi Moriconi[i] Viviana Finato[i] Antonio Mannarino[j] Cristina Grimaldi[j] Filomena Pansa[k] Patrizio Imperiali[k] Carlo Mura[k] Stefano Bianchi[k] Roberto Bigazzi[l]

Departments of Nephrology and Dialysis, [a]Hospital of Versilia, Versilia, [b]Hospital of Lucca, Lucca, [c]Hospital of Massa, Massa, [d]Hospital of Pistoia, Pistoia, [e]University of Pisa, Pisa, [f]Hospital of Pontedera, Pontedera, [g]Hospital of Siena, Siena, [h]Hospital of Poggibonsi, Poggibonsi, [i]Hospital of San Miniato, San Miniato, [j]Hospital of Florence, Florence, [k]Hospital of Arezzo, Arezzo, and [l]Hospital of Livorno, Livorno, Italy

Key Words

Erythropoietin · Erythropoiesis-stimulating agent · Vitamin E · Cytokines · C-reactive protein · Hemodialysis

Abstract

Background: Oxidative stress is prevalent in dialysis patients and has been implicated in the pathogenesis of cardiovascular disease and anemia. Vitamin E is a fat-soluble antioxidant that plays a central role in reducing lipid peroxidation and inhibiting the generation of reactive oxygen species. The aim of this cross-over randomized study was to compare the effects of a vitamin E-coated polysulfone (Vit E PS) membrane and a non-vitamin E-coated polysulfone (PS) membrane on inflammatory markers and resistance to erythropoietin-stimulating agents (ESAs). ***Methods:*** After a 1-month run-in period of standard bicarbonate dialysis with a synthetic membrane, 62 patients of both genders, and older than 18 years, dialysis vintage 48 ± 27 months, BMI 22 ± 3 (from 13 different dialysis units) were randomized (A-B or B-A) in a cross-over design to Vit E PS (treatment A) and to PS (treatment B) both for 6 months. C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations were determined by a sandwich enzyme immunoassay at baseline and every 2 months; red blood cell count, ESA dose and ESA resistance index (ERI) were assessed monthly. ***Results:*** Hemoglobin (Hb) levels significantly increased in the Vit E PS group from 11.1 ± 0.6 g/dl at baseline to 11.5 ± 0.7 at 6 months ($p < 0.001$) and remained unchanged in the PS group. Although ESA dosage remained stable during the observation periods in both groups, ERI was significantly reduced in the Vit E PS group from 10.3 ± 2.2 IU-dl/kg/g Hb week at baseline to 9.2 ± 1.7 at 6 months ($p < 0.001$). No significant variation of ERI was observed in the PS group. A significant reduction in plas-

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Vincenzo Panichi, MD
Departments of Nephrology and Dialysis
Versilia Hospital, Versilia (Italy)
Tel. +39 0584 605 7238, Fax +39 0584 605 9600
E-Mail v.panichi@usl12.toscana.it

ma CRP and IL-6 levels was observed in the Vit E PS group: CRP from 6.7 ± 4.8 to 4.8 ± 2.2 mg/l ($p < 0.001$) and IL-6 from 12.1 ± 1.4 to 7.5 ± 0.4 pg/ml ($p < 0.05$). In the PS group, CRP varied from 6.2 ± 4.0 to 6.4 ± 3.7, and IL-6 from 10.6 ± 2.1 to 9.6 ± 3.5 (p = n.s.). ***Conclusions:*** Treatment with Vit E PS membranes seems to lead to a reduction in ESA dosage in HD patients; in addition, a low chronic inflammatory response may contribute to a sparing effect on exogenous ESA requirements.

Introduction

A pro-oxidative status is highly prevalent in dialysis patients and has been implicated in the pathogenesis of cardiovascular disease, and anemia, and might contribute to increased morbidity and mortality [1, 2].

The uremia-induced oxidation of lipid byproducts, proteins, and nucleic acids [3–5] has several pathophysiological consequences, including enhanced atherogenicity of oxidized low-density lipoproteins [6], as well as accelerated death of circulating erythrocytes, leading to a shorter life span. Red blood cell survival impairs the effect of exogenous recombinant human erythropoietin (rHuEpo) and increases susceptibility to hemolysis due to inflammatory and mechanical causes.

Consequently, the direct scavenging of free radicals through the use of oral vitamin E is an attractive therapeutic strategy. This can be achieved broadly by using oral vitamin E supplementation [7, 8], or more specifically, by binding vitamin E to the dialysis membrane site. Vitamin E (α-tocopherol) was first introduced for this purpose in the late 1990s in the field of hemodialysis (HD) biomaterials to produce a cellulose-based vitamin E-modified dialyzer membrane. Vitamin E, which is well known for being a lipophilic antioxidant of cell membranes and lipoproteins [9], was used as a modifier (or coating agent) on the blood surface of cellulosic hollow-fiber dialyzer membranes. The ultimate goal of using this vitamin was to increase the biocompatibility and to prevent the oxidative stress that is related to leukocyte oxidative burst, and other inflammation-related effects that may result from the interaction between blood constituents and cellulosic fibers [10]. More recently, in order to produce more biocompatible biomaterials, vitamin E has been coated on a polysulfone-based dialysis membrane [11], and this new vitamin E-coated polysulfone membrane has been demonstrated to have a redox capacity and to actively react with redox-active substances in the blood [12].

However, until now, the effects of this new membrane in the management of uremic anemia have been investigated in a limited number of preliminary studies. One preliminary and promising paper has recently been published as pilot study by Andrulli et al. [13], who reported a positive effect of vitamin E-bonded membranes on anemia in hypo-responder dialysis patients

A second recent study shows new positive effects on blood pressure level in dialysed patients using vitamin E membranes [14].

The present study was designed to compare the effects of vitamin E-coated polysulfone (Vit E PS) membranes and a non-vitamin E-coated polysulfone membranes (PS) on inflammatory markers, and resistance to erythropoietin-stimulating agents (ESAs) in a population of chronic HD patients followed up for 1 year.

Patients and Methods

Patients

This 13-month study was conducted in 13 HD centers in Tuscany (Italy) from November 2007 to June 2009. Each participating center followed European Best Practice Guidelines for the management of anemia with regard to rHuEpo and iron utilization [15]. Written informed consent was obtained from each participating patient. Patients older than 18 years with chronic kidney disease stage V and having undergone HD for at least 6 months in the participating HD centers were eligible for inclusion, if their HD regimen was stable. All eligible patients had been on stable ESA therapy for at least 3 months, and had adequate iron stores (ferritin levels 200–400 ng/ml and transferrin saturation 20–40%).

Patients with conditions that could influence cytokine production or ESA requirements, such as acute infection or blood transfusion in the past month, hemoglobinopathies, chronic infection, active immunological disease, immunosuppressive therapy or a history of malignancy were excluded from the study. During the study periods, patients were carefully checked for comorbidities and infections, in particular regarding dialysis access.

Study Design

This was a 13-month, randomized, cross-over, single-blind study (A-B or B-A); after a 1-month run-in period of standard bicarbonate dialysis, patients were centrally randomized in two groups according to the type of treatment. The dialysis technique was randomly assigned with a 1:1 ratio at the beginning of the study by means of a computer-generated random list. Group 1 patients were treated with Vit E PS membranes (treatment A) for 6 months and afterwards they were transferred to PS membranes for another 6 months (treatment B). Group 2 patients, after the run-in period, were treated with PS membranes (treatment B) for 6 months and afterwards they were transferred to Vit E PS membranes (treatment A) for another 6 months.

Clinical Data

The drug and dialysis prescriptions have not been changed during the study. Pre- and postdialysis body weight, blood pressure and heart rate were recorded at baseline and every month. All administered drugs during each dialysis session were recorded, along with all prescribed interdialysis therapies.

Dialysis Modalities

Standard bicarbonate dialysis was performed with low-flux Vit E PS membranes (ViE, Asahi Kasei Kuraray Medical Co Ltd, Tokyo, Japan) or low-flux PS membranes with a surface area ranging from 1.8 to 2.1 m^2 with a blood flow of 320 ± 41 and a dialysate flow of 550 ± 100 ml/min, dialysis time 240 ± 15 min, and a weight loss of 840 ± 90 g/h. The average composition of the dialysate was: sodium 139 mmol/l, potassium 1.5 mmol/l, bicarbonate 39 mmol/l, calcium 1.5 mmol/l, and the dialysate was purified by sterile filtration before entering the dialyzer. Patients were weighed before and after each treatment to determine the volume of ultrafiltration. Net fluid removal was set on an individual basis according to the patient's clinical needs. All HD treatments were carried out with a volumetric control machine allowing for a precise rate of fluid removal. In all centers, analyses of the dialysis water system were performed every 3–6 months, ascertaining the absence of bacteria (<100 colony forming units/ml) or bacteriological contaminant products (endotoxin levels below 0.025 endotoxin units).

Biochemistry

Predialysis serum urea, creatinine, albumin, sodium, potassium, total calcium, phosphate and bicarbonate were measured at the start of the study and at monthly intervals. Serum albumin was measured by means of a nephelometric technique (Dade Behring GmbH, Marburg, Germany) with an intra- and interassay variability of 4.3 and 4.4%, respectively. Hemoglobin (Hb), white cell, lymphocyte, platelet counts and reticulocytes were also assessed monthly. Iron status was evaluated monthly by transferrin saturation and plasma ferritin levels. Equilibrated Kt/V was performed monthly in a mid-week session according to the methods suggested by Daugirdas and Schneditz [16]. Postdialysis urea samples were obtained 10 min after the end of the dialysis session.

Inflammation Parameters

Inflammation parameters were centrally determined bimonthly in patients starting a midweek dialysis session after an overnight fast between 7.00 a.m. and 9:00 a.m. and after 20–30 min of quiet resting in semirecumbent position at baseline. C-reactive protein (CRP) was measured by a high-sensitivity modified laser nephelometry technique (Behring Diagnostics GmbH, Marburg, Germany). The CRP assay was standardized according to the WHO First International Reference Standard and had a sensitivity of 0.1 μg/ml, with a standard reference range of between 0.1 and 0.4 mg/l. Interleukin-6 (IL-6) (Biosource, USA) was measured by a quantitative sandwich enzyme immunoassay technique. Plasma, collected using heparin as anticoagulant, was separated less than 30 min after drawing and stored at –80°C until analysis. Samples were assayed in duplicate and the intra- and inter-assay coefficients of variation for IL-6 were less than 5.3 and 7.2%, respectively. The limit of detection of IL-6 was <5 pg/ml.

Statistics

Continuous data are presented as means ± standard deviation or medians (interquartile ranges) and quartiles, and nominal data are presented as percentages. The difference between mean values was evaluated by the paired-samples t test or by the Wilcoxon signed ranks test for non-normally distributed data; analysis of variance for multiple comparisons was used to analyze differences between the two groups. Spearman's correlation coefficient was calculated for correlation assessments between variables. $p < 0.05$ was taken to be statistically significant.

Endpoints

The primary endpoints were the changes in Hb levels and rHuEpo dosage after Vit E PS or PS membrane use. The ESA resistance index (ERI) was used as a measure of erythropoietin resistance in chronic HD patients, and is calculated by dividing the weekly rHuEpo dose (IU/kg/week) by the hematocrit (%). For the present study, a modified ERI was calculated by dividing the weekly rHuEpo dose (IU/kg/week) by the Hb level (g/dl) [17]. To convert darbepoietin in the equivalent dose of epoietin, the ratio 1:200 (1 μg darbepoietin-α = 200 UI epoietin-α or -β) was used. Hb levels, rHuEpo dosage, and ERI at 2, 4 and 6 months on Vit E PS and PS membranes were compared with baseline. CRP and IL-6 levels at 6 months on Vit E PS and PS membranes were compared with baseline.

Results

Sixty-two chronic HD (34 males and 28 females) patients (mean age 66 ± 13 years, dialysis vintage 48 ± 27 months, BMI 22 ± 3) on regular dialysis treatment 3 times a week for at least 1 year prior to the study were enrolled in this study. Thirty-one patients (mean age 68 ± 13 years; 16 males and 15 females) were assigned to group 1; 31 (mean age 63 ± 11 years; 18 males and 13 females) were assigned to group 2. Sixteen patients had chronic renal failure caused by chronic glomerulonephritis, 6 patients had polycystic kidney disease, chronic pyelonephritis was present in 5 patients, kidney vascular disease in 6 patients, and renal failure of uncertain etiology in the remaining patients.

Fifty-one patients had an arteriovenous fistula and 11 a subcutaneous polytetrafluoroethylene graft. Eight patients experienced significant acute clinical events during the study period and were excluded from the study: 1 surgical nephrectomy, 2 acute myocardial infarctions, 1 vascular surgery for aortic aneurysm, 2 neoplasms, 1 transient ischemic attack, and 1 acute cholecystitis.

The mean Hb level was 11.3 ± 0.6 g/dl (table 1), which was within the normal range according to the European Best Practice Guidelines; there was no relevant difference between the two randomized groups, as the levels were 11.16 ± 0.6 g/dl in group 1 and 11.11 ± 0.7 g/dl in group

Table 1. Demographics, clinical and laboratory characteristics of the study population

		25th percentile	75th percentile
Demographics and clinical characteristics (n = 62)			
Age, years	66 (13)	57	76
Male	34 (54)		
Duration of dialysis, months	48 (27)	20	61
BMI	22 (3)	19.5	25.3
Comorbidities			
Cardivascular disease	21 (33)		
Diabetes	11 (17)		
Hypertension	23 (37)		
Systolic blood pressure, mm Hg	135.2 (21)	120	150
Diastolic blood pressure, mm Hg	74.2 (10.1)	70	80
Vascular access (fistula-graft/CVC)	51 (82)		
Laboratory parameters			
Hb, g/dl	11.3 (0.6)	10.7	12.6
Iron, μg/dl	70.4 (36)	46	84.5
Transferrin, mg/dl	179.9 (48.7)	146	208
Ferritin, ng/ml	496.4 (523)	99.6	764
TSAT	29.4 (17)	17.6	36.5
ERI, UI weekly/kg/g Hb	10.7 (2.08)	9.72	11.8
Albumin, g/dl	3.7 (0.4)	3.4	4
Use of statins	19 (30)		
Smoking habit	10 (16)		

Continuous variables are expressed as mean (standard deviation) or median (IQR) and 25–75th percentiles. Categorical variables are expressed as number and percentage of total study population.

2 (p = n.s.). The variables related to iron status (transferrin saturation and ferritin levels) were also within the desired range, without any difference between the two groups. Seven patients were not treated with intravenous iron. Mean ERI in the population was 10.3 IU/kg·g Hb/week with no between-group difference.

ESA Requirements

Changes in Hb level, rHuEpo dosage and ERI during the study are shown in figures 1–3. The mean Hb level significantly increased from 11.1 ± 0.6 g/dl at baseline to 11.5 ± 0.7 g/dl after 6 months ($p < 0.001$, vs. baseline) on Vit E PS membranes. The rHuEpo dosage remained stable: 6.833 ± 5.865 IU/week at baseline and 6.983 ± 5.679 IU/week after 6 months on Vit E PS membranes (p = n.s.). The mean ERI decreased from 10.3 ± 2.2 IU-dl/kg/g Hb week at baseline to 9.3 ± 1.7 after 6 months on Vit E PS membranes ($p < 0.001$).

The mean Hb level remained unchanged: 1.2 ± 0.6 g/dl at baseline and 11.1 ± 0.7 g/dl after 6 months (p < n.s. vs. baseline) on the PS. The rHuEpo dosage remained stable: 6.833 ± 5.865 IU/week at baseline and 6.983 ± 5.679 IU/week after 6 months on PS membranes (p = n.s.). The mean ERI slightly decreased from 10.4 ± 2.3 IU-dl/kg/g Hb week at baseline to 10.2 ± 1.8 after 6 months on PS membranes (p = n.s.).

Inflammatory Markers

A significant reduction in plasma CRP and IL-6 levels was observed on Vit E PS membranes: CRP from 6.7 ± 4.8 to 4.8 ± 2.2 mg/l ($p < 0.001$) and IL-6 from 12.1 ± 1.4 to 7.5 ± 0.4 mg/l ($p < 0.05$). In the PS group, CRP varied from 6.2 ± 4.0 to 6.4 ± 3.7, and IL-6 varied from 10.6 ± 2.1 to 9.6 ± 3.5 (p = n.s.) (fig. 4). During the 6-month follow-up period, no significant correlations were found between decreases in inflammatory markers and decreases in ERI in the Vit E PS group.

Discussion

The results of this multicenter, randomized, clinical trial suggest that the presence of vitamin E on the blood side of a highly biocompatible polysulfone membrane dialyzer has a significant positive effect on ESA resistance compared with the same dialyzer used in the absence of vitamin E. A number of studies have looked at the effect of vitamin E on various anemia parameters [18–20], and the great majority of them were in line with our own findings. Most of these studies have been performed using a modified cellulose-based membrane (VECM). When dialyzed with VECMs, 38 HD patients were able to maintain their prior Hb levels on half their previous rHuEpo dosage [18]. A close direct linear relationship between plasma α-tocopherol levels and Hb [21] was also reported. Other authors have also noted an ability to maintain the patients' Hb on comparatively lower rHuEpo dosages [22, 23] or even after complete withdrawal of rHuEpo while on VECM dialysis. In another study, Nakatan et al. [19] observed a statistically significant increase in Hb from 9.5 to 10.7 g/dl after switching patients to VECMs, without a significant change in rHuEpo dosage. There was no change in reticulocyte count, suggesting that the improvement in Hb was not due to increased hematopoiesis. These Japanese authors speculated that this was due to better red blood cell survival, as supported by the prolonged red blood cell lifespan demonstrated in their study, as well as in other studies [18, 21]. When patients

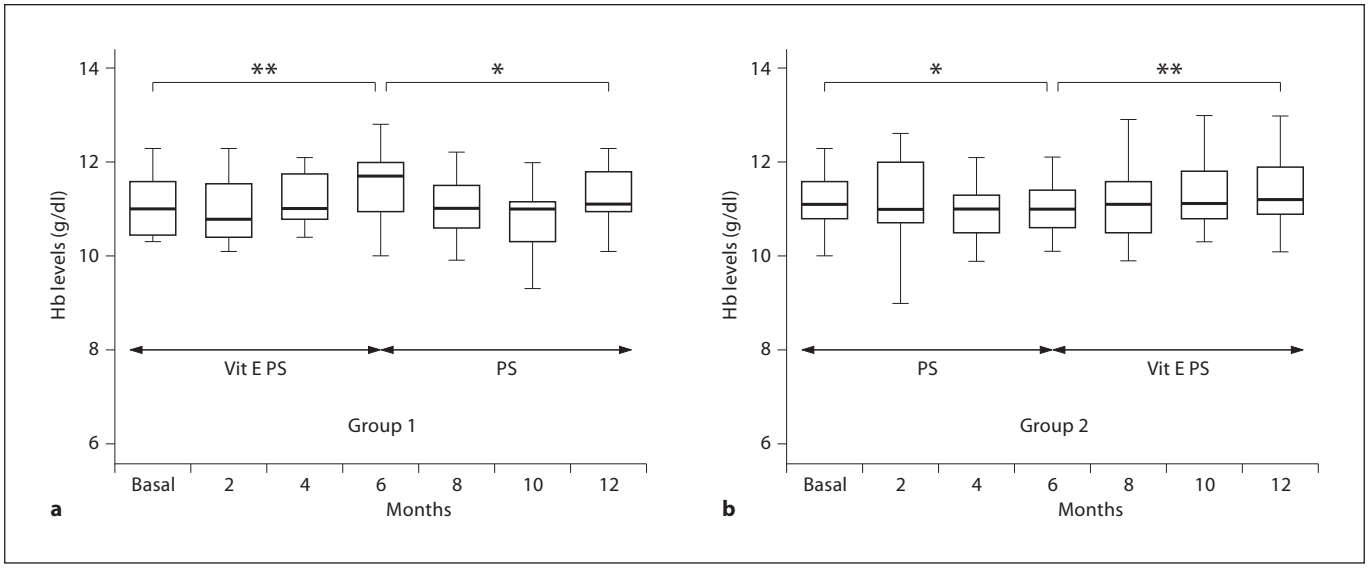

Fig. 1. a Hb levels (medians, interquartile ranges and outliers) during follow-up for group 1 (Vit E PS – PS). **b** Hb levels (medians, interquartile ranges and outliers) during follow-up for group 2 (PS – Vit E PS) are reported. * $p < 0.05$ basal vs. 6 months; ** $p < 0.001$ baseline vs. 6 months (paired sample t test).

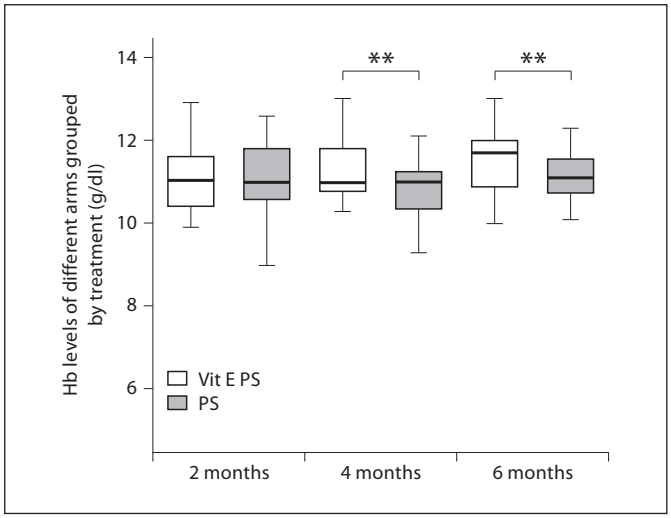

Fig. 2. Hb levels (medians, interquartile ranges and outliers) of different arms grouped by treatment. Hb levels were significantly different at 4 and 6 months. ** $p < 0.001$ baseline vs. 4 and 6 months.

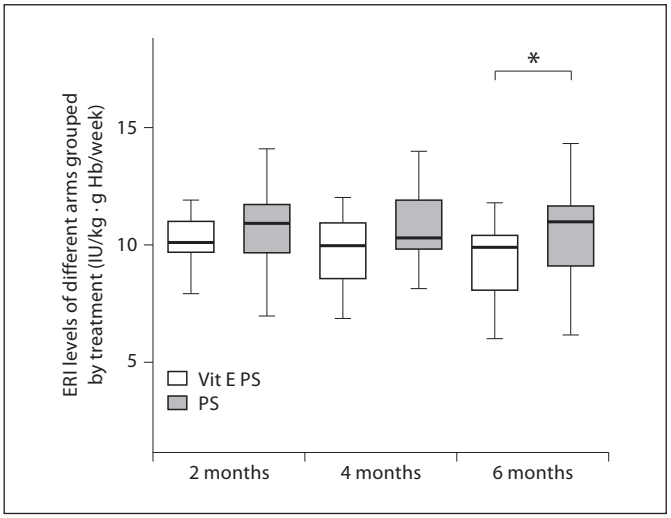

Fig. 3. ERI levels (medians, interquartile ranges and outliers) of different arms grouped by treatment. ERI levels were significantly different at 6 months. * $p < 0.05$ baseline vs. 6 months.

switched back to their previous polysulfone dialyzer, there was a downward trend in Hb and hematocrit which required an increase in rHuEpo dosage [19]. The improved red blood cell survival may be the consequence of a decrease in dysmorphic erythrocytes, and improved red blood cell rheology and viscosity with the use of VECMs, resulting in less hemolysis [23]. The exact mechanism leading to better blood counts and the cause of the increase in reticulocyte count remain unclear, as observed in other studies [21, 24]. It is likely that multiple

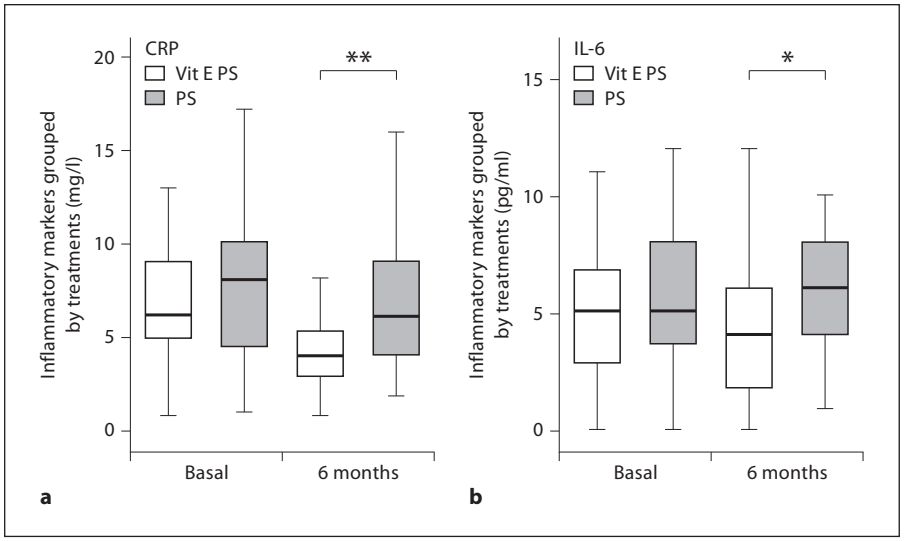

Fig. 4. Changes in inflammatory parameters during the study (medians, interquartile ranges and outliers). A significant reduction in plasma CRP and IL-6 levels was observed during Vit E PS treatment after 6 months. No significant changes were observed on PS treatment. * $p < 0.05$ vs. baseline; ** $p < 0.001$ vs. baseline.

mechanisms are involved. In the majority of cases, these favorable hematologic changes were seen in association with increased levels of plasma or erythrocyte vitamin E, as well as lower levels of oxidative stress, as represented by oxidized low-density lipoprotein, asymmetric dimethylarginine, malondialdehyde and malondialdehyde-low-density lipoprotein [25]. However, other studies have shown conflicting results. Notwithstanding lower malondialdehyde levels, a small study failed to demonstrate significant changes in Hb, hematocrit, or rHuEpo dosages on VECMs [26]. Another study demonstrated a larger amount of unsaturated fatty acids in the red blood cell membrane, compatible with reduced oxidative stress, and erythrocytes demonstrated enhanced resistance to hemolysis after 6 weeks of dialysis with VECMs [20]. However, this reverted to baseline levels by 13 weeks.

More recently, Cruz et al. [27], in an open-label multicenter study, showed interesting data in 172 stable chronic HD patients that were shifted from their previous dialyzer to VECMs for 1 year. A significant increase in Hb levels was observed on VECMs with a parallel decrease of rHuEpo dosage; as possible mechanisms of these positive effects, the authors suggested enhanced membrane biocompatibility, reduced oxidative stress and inflammation with VECMs, resulting in improved red blood cell survival and/or rHuEpo responsiveness.

Recently, the evolution of HD technology toward more biocompatible biomaterials has stimulated industries to produce Vit E PS membranes that will replace the cellulosic ancestor. This new generation of dialyzer membranes has been introduced in the clinical practice in Japan and Europe, and early clinical evidence of improved biocompatibility and oxidative stress index was reported in a controlled trial performed with a previous version of these modified membranes [28].

However, in our cross-over randomized study we compared, for the first time, this new Vit E PS membrane to PS and assessed ESA resistance and plasma levels of inflammatory markers. It is well known that in HD patients anemia is linked to inflammation and oxidant stress associated with the uremic syndrome [29]; moreover, chronic kidney disease patients may require much higher doses of ESAs than usual in order to maintain the recommended Hb target of 11 g/dl or above [30]. In the last few years, several small clinical trials have reported the positive effect of vitamin E-coated membranes on surrogate markers of oxidative stress and inflammation in HD patients [reviewed in ref. 31]. In this study, a significant reduction in plasma CRP was observed on Vit E PS dialysis; the reduction in the dialysis-induced chronic inflammatory response may contribute to a sparing effect on exogenous ESA administration. According to these data, the reduced ESA requirement on Vit E PS dialysis may be due to the longer red blood cell survival and improved rheology resulting from reduced oxidative stress and inflammation, as suggested by the lower mean erythropoietin index in patients after they were shifted to Vit E PS membranes. Inflammation is strongly associated with erythropoietin resistance, as defined by a high erythropoietin index, in HD and PD patients [32].

Finally, apart from their apparent antioxidant activity, Vit E PS membranes have also been shown to be more

biocompatible than equivalent unmodified membranes, likely ameliorating the inflammatory stress associated with the HD procedure.

There are some limitations that need to be mentioned.

Firstly, patients received either epoietin-α or darbopoietin, and this may be misleading; however, all patients received the same ESAs during the study period and the change of ESAs was considered an exclusion criterion. Furthermore, in this study patients with mild chronic inflammation were evaluated; future studies are needed to evaluate Vit E PS membranes in patients with more marked inflammation.

In conclusion, this study suggested that these membranes may play an effective role in the management of uremic anemia and lead to a reduction in the chronic low-grade inflammatory response of patients with uremic syndrome. Such beneficial effects are of particular relevance in clinical practice. Further studies of Vit E PS membranes currently available for clinical use are in progress and the great majority of these preliminary data indicate that these membranes can ameliorate the management of anemia as a result of improved erythropoietin responsiveness in maintenance HD patients.

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