Effect of vitamin E-bonded dialyzer on eosinophilia in haemodialysis patients

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Abstract

Background. Eosinophilia in haemodialysis patients probably results from allergy to haemodialysis-related materials, including dialyzer membranes. We examined the effects of vitamin E-bonded dialyzers on eosinophil counts in haemodialysis patients.

Methods. We enrolled seven patients who were on regular haemodialysis and had sustained eosinophilia. White blood cell, eosinophil, CD4- and CD8-positive lymphocyte counts, and serum interleukin-5 (IL-5) and IgE levels were determined before, 2 and 4 weeks after switching to vitamin E-bonded dialyzers.

Results. Eosinophil and CD4-positive lymphocyte counts and serum IL-5 were significantly (P = 0.003, 0.003 and 0.031, respectively) decreased after switching to vitamin E-bonded dialyzers. CD8-positive lymphocyte counts and serum IgE levels were unaltered. Crossover tests in two cases reproduced the higher eosinophilia within 4 weeks after returning to the original non-vitamin E-bonded dialyzer.

Conclusion: Vitamin E-bonded dialyzers may ameliorate eosinophilia through a mechanism mediated by a decrease in IL-5 secretion by CD4-positive lymphocytes.

Keywords: CD4-positive lymphocyte; eosinophilia; haemodialysis; IL-5; vitamin E-bonded dialyzer

Introduction

It has been reported that haemodialysis-related eosinophilia occurs in 13–25% of the haemodialysis population [1–4]. The mechanisms of this phenomenon, however, are not fully understood, though a kind of allergic reaction to haemodialysis-related materials has been proposed as etiology [4]: some kind of allergen is first processed by antigen-presenting cells, followed by the activation of CD4-positive lymphocytes, resulting in the releasing of cytokines, including interleukin-5 (IL-5). IL-5 is essential for the differentiation of eosinophils in bone marrow. The activated mature eosinophils release granular proteins, such as major basic protein, eosinophil cationic protein and eosinophil peroxidase, which in turn produce leukotrienes [5–7]. It is presumed that these chemical mediators somehow damage a variety of cells and tissues.

The vitamin E-bonded dialyzer developed recently has been shown to reduce haemodialysis-associated oxidative stress [8–10] and to improve biocompatibility in the haemodialysis environment [11]. The purposes of the present study were to determine whether vitamin E-bonded dialyzers could ameliorate the eosinophilia seen in haemodialysis patients and to identify the underlying mechanism(s) of haemodialysis-related eosinophilia.

Subjects and methods

Patients’ profiles

For this study we selected seven patients who were on regular haemodialysis and had sustained eosinophilia (>700 per microlitre). Their mean age was 60.0 ± 10.8 years. The end-stage renal diseases of these patients resulted from chronic glomerulonephritis (n = 4), diabetic nephropathy (n = 2) or renal tuberculosis (n = 1). Their mean time on haemodialysis was 5.8 ± 3.7 years. All patients had 4 h haemodialysis sessions three times weekly, with a dialysate flow rate of 500 ml/min. The protocol of the study was approved by the ethics committee of our institution, and all patients gave their written informed consent to enter the study.

The dialyzer membranes in use when the patients’ eosinophilia was documented were cuprammonium rayon (n = 2), cellulose diacetate (n = 1), cellulose triacetate (n = 2) and polymethylmethacrylate (n = 2). All materials used in...
Dialysis were steam-sterilized. Heparin was used in all the patients as anticoagulants. During dialysis, no patient had eosinophilia-related symptoms such as eruption and itching. Possible causes of eosinophilia, such as parasitic disease, bronchial asthma, collagen disease and adverse reaction to drugs, were excluded. All patients showed normal levels of serum C-reactive protein (0.22±0.10 mg/dl), suggesting the absence of systemic inflammation. Serum albumin was 3.66±0.50 g/dl and serum ferritin 267±102 ng/ml (normal 17–291 ng/ml). Medications and their dosages were not changed during the study.

**Study design**

After baseline data were documented, the dialyzers were replaced with ones equipped with vitamin E-bonded elements (CL-EE; Asahi Kasei Medical Co., Tokyo, Japan), with comparable membrane areas and performance, and haemodialysis was otherwise continued under the same conditions as described above. Blood was drawn before dialysis sessions to measure white blood cell, eosinophil, CD4- and CD8-positive lymphocyte counts, and serum IL-5 and IgE levels. These parameters were measured before and 2 and 4 weeks after switching to vitamin E-bonded dialyzers.

In a crossover test, performed in two cases, the dialyzers were reverted to the original ones (cellulose triacetate membranes) after the testing with the vitamin E-bonded dialyzers, and blood tests were repeated 4 weeks after the reversion.

White blood cell and its fractions were counted with an automated cytometer; CD4- and CD8-positive lymphocytes, with a flow cytometer (Epics XL, Beckman Coulter Inc., CA). The serum level of IL-5 was determined by an IL-5 EIA kit (MBL, Nagoya, Japan), and of IgE by nephelometry, using N-latex IgE II (Dade Behring Inc., IL).

**Statistical analysis**

All data are expressed as mean±SD. Sequential data in individuals were analysed by repeated measures ANOVA, and when significant, values at any two points were analysed by paired Student’s t-tests. The values of white blood cells and eosinophil counts and of serum IL-5 levels were transformed to logarithmic values to achieve normal distribution of the data. A P-value<0.05 was considered significant.

**Results**

**White blood cell, eosinophil and CD4- and CD8-positive lymphocyte counts**

Although white blood cell counts were not changed (9600±4743 to 6557±1632 per microlitre; P=0.11), eosinophil counts were significantly decreased from 4627±4773 to 896±784 per microlitre at 4 weeks after switching to vitamin E-bonded dialyzer (P=0.003) (Figure 1a). CD8-positive lymphocytes were not reduced (462±142 to 394±133 per microlitre, P=0.12), but CD4-positive lymphocytes were significantly reduced (692±242 to 556±205 per microlitre, P=0.003) after switching to vitamin E-bonded dialyzers (Figure 1b). Other fractions of white blood cells did not show any changes (neutrophils, 3021±1344 to 3871±1715 per microlitre, P=0.13; monocytes, 303±170 to 389±176 per microlitre, P=0.31; basophils, 62±71 to 86±65 per microlitre, P=0.59).

**Serum IL-5 and IgE levels**

The mean value of serum IL-5 before switching to vitamin E-bonded dialyzers was 19.1±16.5 pg/ml (normal <10.0 pg/ml). At 4 weeks after switching to vitamin E-bonded dialyzers, the serum IL-5 was significantly decreased to 6.4±7.7 pg/ml (P=0.031) (Figure 1c). On the other hand, serum IgE was not changed (114±178 to 123±141 IU/ml, normal <165 IU/ml, P=0.50) by the change to vitamin E-bonded dialyzers.

**Correlation between serum IL-5 and eosinophil counts**

A significant positive correlation was found between serum IL-5 levels and eosinophil counts (r=0.56,
The results of crossover tests performed in two cases are shown in Figure 2. In each case, eosinophil counts and serum IL-5 levels, both of which had decreased during dialysis with vitamin E-bonded dialyzers, were re-elevated 4 weeks after resuming dialysis with the original dialyzers.

**Crossover tests**

The results of crossover tests performed in two cases are shown in Figure 2. In each case, eosinophil counts and serum IL-5 levels, both of which had decreased during dialysis with vitamin E-bonded dialyzers, were re-elevated 4 weeks after resuming dialysis with the original dialyzers.

**Discussion**

Eosinophilia in haemodialysis patients is frequently observed, as reported in the literature [1–4]. The data from our haemodialysis unit reveal the relatively low incidence of eosinophilia, 4.5%, probably due to the non-use of ethylene oxide gas or the introduction of polysulfone dialyzers. Eosinophilia may have been induced by an allergic reaction to haemodialysis-related materials, such as ethylene oxide, in the past; and the resultant increase in eosinophils might cause allergic symptoms, such as eruption, itching, respiratory impairment and myocarditis [1–3]. Our patients did not have eosinophilia-related symptoms and signs. Although none of the patients in this study were treated with materials sterilized with ethylene oxide gas, their eosinophilia could be ascribed to dialyzer membrane materials because the eosinophilia had not been observed prior to initiation of haemodialysis.

In the present study, vitamin E-bonded dialyzers ameliorated eosinophilia in all the patients tested, and reduced CD4-positive lymphocyte counts and serum IL-5 levels. A crossover study (on two cases) reproduced the eosinophilia and the elevation of serum IL-5 and the CD4-positive lymphocyte count. These results strengthen the notion that vitamin E-bonded dialyzers could ameliorate eosinophilia. Vitamin E-bonded dialyzers were developed to protect from the oxidative stress of haemodialysis and increase dialyzer biocompatibility. Recent studies reported that this membrane improves dialysis-induced leukocytopenia [11], myeloperoxidase release [12], endothelial dysfunction [13] and renal anaemia [14,15], just as it improves markers of oxidant stress [11–14].

Whether the vitamin E-bonded dialyzer increases the plasma level of vitamin E remains a controversial question. Some investigators have reported that vitamin E-bonded dialyzers exert an antioxidant effect by elevating plasma vitamin E levels [10,11]. Mune et al. [16] failed to find such an increase in plasma vitamin E levels during the use of vitamin E-bonded dialyzers, in spite of a significant attenuation of oxidant stress. We did not evaluate plasma levels of antioxidant makers or vitamin E.

Vitamin E has recently been recognized as an immunomodulator in addition to an antioxidant. Zheng et al. [17] reported that dietary vitamin E supplementation suppresses nasal allergic reactions by decreasing IL-5 production. Moreover, vitamin E-bonded dialyzers have been demonstrated to attenuate excess production of cytokines by CD4-positive lymphocytes [18]. Thus, the vitamin E-bonded membrane might ameliorate eosinophilia by decreasing the IL-5 secretion of CD4-positive lymphocytes, as suggested by our present study.

In conclusion, this study showed that vitamin E-bonded dialyzers ameliorated eosinophilia in haemodialysis patients, and reduced CD4-positive lymphocytes and serum IL-5 as well. Vitamin E-bonded dialyzers might be valuable in the treatment of dialysis-related eosinophilia, which may sometimes be harmful.

**Conflict of interest statement.** None declared.

**References**


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