A randomized controlled trial evaluating the erythropoiesis stimulating agent sparing potential of a vitamin E-bonded polysulfone dialysis membrane

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**ABSTRACT**

**Background.** Vitamin E (VE) bonded polysulfone dialysis membranes have putative erythropoiesis stimulating agent (ESA)-sparing and anti-inflammatory properties based on data from a small number of studies. We sought to investigate this in a large, prospective 12-month randomized controlled trial.

**Methods.** Two-hundred and sixty prevalent haemodialysis (HD) patients were randomized to dialysis with VE-bonded polysulfone membranes or non-VE-bonded equivalents. All ESA-dosing was performed by means of a computer-based anaemia management decision support system. Monthly data were used to calculate the ESA resistance index (ERI) and blood tests were performed at baseline, 6 and 12 months for measurement of C-reactive protein (CRP) levels.

**Results.** Of the 260 patients, 123 were randomized to dialysis with the VE-membrane and 12-month data was available for 220 patients. At the study population level, no beneficial effect of the VE membranes on the ERI or CRP levels was observed. Post hoc analyses indicated that there was a significant fall in ERI for patients with the highest baseline ESA resistance dialysed with the VE (9.28 [7.70–12.5] versus 7.70 [5.34–12.7] IU/week/kg/g/dL Hb, P = 0.01) but not the control membranes (9.45 [7.62–12.3] versus 8.14 [4.44–15.6] IU/week/kg/g/dL Hb, P = 0.41); this was not attributable to changes in CRP levels.

**Conclusions.** Wholesale switching of all chronic HD patients to dialysis with VE-bonded polysulfone membranes appears not to be associated with improvements in ESA-responsiveness or CRP. These membranes may have utility in patients with heightened ESA resistance.

**Keywords:** anaemia, haemodialysis, inflammation, vitamin E
INTRODUCTION

A number of factors conspire to cause anaemia in haemodialysis (HD) patients. Reduced levels of circulating erythropoietin [1], altered iron handling [2] and increased levels of oxidative stress [3, 4] and inflammation [5] are key. Blood/membrane interactions are thought to be important contributors to the latter two. Vitamin E (VE) bonded membranes have been developed because of the anti-oxidant and anti-inflammatory properties of VE [6] which, in turn, may reduce erythropoiesis stimulating agent (ESA) requirements.

Several studies evaluating the use of VE-bonded modified cellulosic membranes have reported improvements in renal anaemia parameters [7–12] and markers of inflammation [13–15]. More recently, VE-bonded versions of modern bio-compatible polysulfone membranes have been developed. Their effect on renal anaemia has only been studied in a relatively small number of patients to date [16–21]. In the present study, we evaluated the potential of VE-bonded polysulfone membranes to improve renal anaemia and reduce inflammation in a large prospective 12-month randomized controlled trial of prevalent HD patients. Our control membrane was identical to the VE-coated device thus eliminating potential confounding from other membrane-related factors.

MATERIALS AND METHODS

All chronic adult HD patients using our service were screened for study participation. Patients who had been established on HD for >3 months and who were on a thrice weekly dialysis schedule were eligible for inclusion. Patients were excluded if they relied on regular blood transfusions, required a 2.5 m<sup>2</sup> dialysis membrane (no VE-equivalent available), had a significant inflammatory illness [defined as C-reactive protein (CRP) >50 mg/L or 3× the patient’s baseline in the previous 3 months], or if they were expected to stop HD in <6 months. All patients provided written informed consent and independent language translators were used for non-English speakers. The trial protocol, patient information leaflet and consent form were approved by the local research ethics committee (reference 08/H1307/144). The study was registered prospectively on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) (reference: 2009-017505-11) and International Standard Randomised Controlled Trial Number (reference: 12650766) databases and was adopted onto the National Institute for Health Research portfolio (reference: 6789).

Study participants were randomized to HD with either a VE-bonded high-flux polysulfone membrane (VIE-A, Asahi Kasei Medical Corporation Limited, Japan) or an identical non-VE-bonded high-flux polysulfone membrane (Rexeed-A, Asahi Kasei Medical Corporation Limited, Japan). Patients were followed prospectively for 12 months, or until they left the study, and monthly haemoglobin levels and ESA doses were recorded. Pre-dialysis blood tests were performed at baseline, 6 and 12 months for measurement of CRP levels using a highly sensitive assay.

RESULTS

Patients

A total of 500 HD patients were screened for the study and, of the 348 eligible patients, 260 patients were enrolled. The principal reasons for ineligibility were the presence of inflammation (n = 55), requirement for a large surface area dialyser (n = 37), patients not on a thrice weekly dialysis schedule (n = 27), established on HD for <3 months (n = 12) or imminent switch of treatment modality planned (n = 9). Of the eligible patients, the principal reason for non-participation in the study was declined consent (n = 80). Of the 260 enrolled patients, 123 were randomized to dialysis with the VE membrane. Patients were followed for 12 months and 220 completed the study. The main reasons for study discontinuation were death or renal transplantation (Figure 1).

As shown in Table 1, the patients were well matched at baseline with the exception of a higher proportion of patients with diabetes (35% versus 23%; P = 0.03) and a higher median

All patients requiring an ESA were prescribed Darbepoetin alfa (Amgen) and dosing was carried out by means of a computer-based predictive algorithm that we have previously demonstrated provides a stable platform to test the effects of population interventions [22]. The predictive algorithm recommended ESA dose adjustments based on the actual haemoglobin level and its trajectory with a target haemoglobin level of 11.5 g/dL, the midpoint of the target haemoglobin range recommended by the National Institute for Health and Clinical Excellence at the time the study was conducted [23]. All patients received protocolized prescription of intravenous iron based on their haemoglobin, ferritin and CRP levels, mean red cell volume and the percentage of hypochromic red blood cells (%RCH).

We used the ESA resistance index (ERI) as the primary outcome measure to permit comparison with other studies examining the effects of VE bonded membranes on ESA requirements [16, 18, 19, 21]. The ERI was defined as the weekly ESA dose (IU) divided by the product of the patient’s weight (kg) and the haemoglobin level (g/dL). A conversion ratio of 1:200 was used to convert the darbepoetin dose (μg) to international units (IU) of erythropoietin as per convention [24, 25].

Pairwise comparisons of continuous variables between study groups were performed using a t-test or Mann–Whitney U test depending on the underlying distribution. Categorical variables were compared using a Chi-squared test or Fisher’s exact test as appropriate. Baseline and 12-month values of continuous variables were compared within groups using either the paired sample t-test or the Wilcoxon-signed ranks test. The influence of time and study group allocation was assessed by repeated measures ANOVA. For the CRP levels, this was performed on log-transformed data which approximated a normal distribution. Statistical analyses were carried out using Stata 12 (Stata Corporation, Texas, USA) and SPSS version 16.0 (IBM Corporation, New York, USA). Statistical significance was set at the 5% level.
post-dialysis weight (73.4 [61.2–87.0] versus 69.7 [56.7–79.0] kg; P = 0.03) in the VE group. In terms of the baseline anaemia parameters detailed in Table 2, the only significant difference was a higher median unadjusted ESA dose in the VE group (20 [7.5–30] versus 20 [10–40] μg/week; P = 0.049). Given the higher median weight in the VE group and the positive correlation between weight and ESA dose [Spearman’s rank correlation coefficient (r) = 0.19, P < 0.01], the weight-adjusted ESA doses were compared between groups and found not to differ (P = 0.16).

**Haemoglobin**

The mean monthly haemoglobin levels for the two study groups are shown in Figure 2. There were no significant differences between the groups at baseline (P = 0.09) or 12 months (P = 0.98). Pairwise comparisons of the mean baseline and 12-month haemoglobin levels revealed no significant differences in either the control group (P = 0.12) or the VE group (P = 0.64). Additionally, a repeated-measures ANOVA found no significant effect of time (P = 0.44), study group (P = 0.33) or significant interaction between time and study group (P = 0.38). There were no statistically significant differences between the groups in the indices of iron status measured, i.e. ferritin levels and %RCH, at baseline or 12 months, nor when the 12-month changes in each of these parameters were compared between study groups (P > 0.2 in all cases). There were no significant differences between the groups in the doses of iron received at baseline or 12 months (P > 0.2 in both cases). (See Supplementary data for more details.)
Table 1. Baseline patient characteristics

|                  | Control | Vitamin E | P  |
|------------------|---------|-----------|----|
| N                | 137     | 123       |    |
| Sex              |         |           |    |
| Male             | 80 (58%)| 76 (62%)  | 0.58|
| Female           | 57 (42%)| 47 (38%)  |    |
| Age (years)      | 64.0 (1.3) | 62.6 (±1.5) | 0.50|
| Ethnicity        |         |           |    |
| White            | 106 (77%) | 93 (76%)  | 0.96|
| Asian            | 24 (18%) | 22 (18%)  |    |
| Black            | 6 (4%)   | 7 (6%)    |    |
| Other            | 1 (1%)   | 1 (1%)    |    |
| Time on renal replacement therapy (years) | 3.9 [1.8–7.6] | 3.2 [1.2–6.6] | 0.18|
| Dialysis access, n (%) |         |           | 0.13|
| Fistula          | 109 [80%] | 109 [89%] |    |
| Dialysis catheter| 25 [18%] | 13 [11%]  |    |
| Graft            | 3 [2%]   | 1 [1%]    |    |
| Pre-dialysis systolic blood pressure (mmHg) | 135 [±2.1] | 139 [±2.2] | 0.18|
| Pre-dialysis diastolic blood pressure (mmHg) | 71 [±1.2] | 72 [±1.5]  | 0.75|
| Weight (kg)      | 69.7 [56.7–79.0] | 73.4 [61.2–87] | 0.03|
| Cause of ESRF, n (%) |         |           | 0.54|
| Diabetes         | 27 (20%) | 30 (24%)  |    |
| Autosomal dominant polycystic kidney disease | 9 (7%) | 9 (7%) |    |
| Chronic pyelonephritis | 10 (7%) | 8 (7%) |    |
| Glomerulonephritis | 30 (22%) | 16 (13%) |    |
| Hypertension     | 14 (10%) | 10 (8%)   |    |
| Renal vascular disease | 12 (9%) | 8 (7%) |    |
| Other            | 16 (12%) | 19 (15%)  |    |
| Unknown          | 19 (14%) | 23 (19%)  |    |
| Co-morbidity, n (%) |         |           |    |
| Diabetes         | 31 (23%) | 43 (35%)  | 0.03|
| Ischaemic heart disease | 43 (31%) | 31 (25%) | 0.27|
| Peripheral vascular disease | 37 (27%) | 34 (28%) | 0.91|

Data presented as mean [±standard error] or median [interquartile range] unless stated.

Table 2. Baseline anaemia parameters

|                   | Control       | Vitamin E      | P   |
|-------------------|---------------|----------------|-----|
| Haemoglobin (g/dL)| 11.7 [±0.1]   | 11.4 [±0.1]    | 0.09|
| Mean corpuscular volume (fL) | 97 [±0.6]  | 96 [±0.5]    | 0.32|
| Red cell hypochromasia (%) | 5 [2–9] | 4 [2–9]   | 0.30|
| Packed cell volume (%) | 37 [±0.4] | 36 [±0.4]    | 0.26|
| Darbepoetin alfa dose (μg/week) | 20 [7.5–30] | 20 [10–40] | 0.049|
| Weight-adjusted Darbepoetin alfa dose (μg/kg/week) | 0.25 [0.13–0.40] | 0.28 [0.14–0.45] | 0.16|
| ESA resistance index (ERI) (IU/week/kg/g/dL Hb) | 3.96 [3.45–4.96] | 5.06 [2.33–8.09] | 0.13|
| Patients not requiring ESA at baseline, n (%) | 13 [9.5%] | 8 [6.5%] | 0.38|
| Ferritin (μg/L)   | 490 [±20]    | 460 [±19]     | 0.26|
| Iron sucrose dose (mg/week) | 25 [25–50] | 25 [25–50] | 0.24|

ESA, erythropoiesis stimulating agent; Hb, haemoglobin.
Data presented as mean [±standard error] or median [interquartile range] unless stated.

**ESA resistance index**

The median monthly ERIs for the two study groups are shown in Figure 3. There were no significant differences between the groups at baseline (P = 0.13) or at 12 months (P = 0.20), nor any significant differences when the baseline and 12-month medians were compared in the control (P = 0.30) or VE (P = 0.60) groups. Similarly, a comparison of the 12-month change in ERI found no statistically significant difference between the control and VE groups (P = 0.08), as shown in Figure 4. These analyses were repeated after stratifying patients on the basis of diabetic status and the between-group differences remained non-statistically significant in all cases.

The median ERI in the present study was lower than that reported in previous studies [17–21]; therefore, post hoc analyses after stratifying patients into tertiles of baseline ERI were performed. There was an even distribution of patients randomized to each membrane across the tertiles of ERI (P = 0.18) and the between-group comparisons of ERI at baseline and at 12 months were non-significant across all three tertiles as shown in Table 3. After 12 months, the median ERI of patients in the lowest tertile increased, irrespective of study.
group, and the ERI in the middle tertile remained unchanged (Figure 5). There was a reduction in the ERI for those patients with the highest ESA resistance at baseline dialysing with the VE-bonded (P = 0.01), but not the control (P = 0.41), membranes as shown in Figure 5.

As there appeared to be a differential effect of the VE membrane depending on the baseline ERI, a regression model for the 12-month change in ERI was constructed comprising the variables coding for baseline ERI and study group in addition to an interaction term for these two variables. The regression coefficient for the interaction term was statistically significant (P < 0.01) suggesting an effect of the VE membrane on the change in ERI after 12 months conditional on the baseline ERI. This is depicted graphically in Figure 6, which is a scatter plot of the change in ERI against the baseline ERI and best-fit linear regression lines through the data points for each of the two study groups. The best-fit regression line for the control group did not differ significantly from zero (P = 0.30), whereas the regression line for the VE group had a negative slope (β = -0.30 [±0.07]) and differed significantly both from zero and from the control group regression line (P < 0.01 in both cases). Given the higher proportion of patients with diabetes in the VE group, the regression analysis was repeated after adjusting for the presence of diabetes. In this analysis the

Table 3. Baseline and 12-month ESA resistance indices for study patients, stratified by ERI at baseline and study group

|                      | Baseline          | 12 months         | P*      |
|----------------------|-------------------|-------------------|---------|
|                      | n                 | ERI (IU/week/kg/g/dL Hb) | n     | ERI (IU/week/kg/g/dL Hb) |         |
| Highest ERI tertile  |                   |                   |         |
| Control              | 39                | 9.45 [7.62–12.3]  | 31     | 8.14 [4.44–15.6]  | 0.41    |
| Vitamin E            | 48                | 9.28 [7.70–12.5]  | 41     | 7.70 [5.34–12.7]  | 0.01    |
| P                   | 0.72              |                   | 0.60   |                   |         |
| Middle ERI tertile   |                   |                   |         |
| Control              | 50                | 4.40 [3.53–5.45]  | 45     | 4.04 [2.60–6.02]  | 0.87    |
| Vitamin E            | 36                | 4.70 [3.83–5.36]  | 31     | 5.18 [3.04–6.56]  | 0.49    |
| P                   | 0.50              |                   | 0.60   |                   |         |
| Lowest ERI tertile   |                   |                   |         |
| Control              | 48                | 1.66 [0.000–2.23] | 40     | 1.91 [0.351–3.50] | 0.02    |
| Vitamin E            | 39                | 1.53 [0.603–2.30] | 32     | 2.13 [1.28–3.55]  | 0.03    |
| P                   | 0.84              |                   | 0.52   |                   |         |

Data presented as median [interquartile range].

*P-value for baseline versus 12 months.

†P-value for between-group comparisons.
Regression coefficient for the interaction term remained statistically significant (P < 0.01).

C-reactive protein

The baseline CRP levels were similar between the study groups at baseline and 12 months (P = 0.29 and P = 0.84, respectively) as shown in Figure 7. The CRP levels at 12 months did not differ significantly from the baseline levels in either group (P > 0.25 in both cases) nor did the 12-month change in CRP levels differ between groups (P = 0.68) as shown in Figure 8. A repeated-measures ANOVA identified that the log-transformed CRP levels changed significantly across study visits (P < 0.001) but there was no significant effect of study group (P = 0.47) nor significant interaction between study group allocation and time (P = 0.87).

The CRP levels were analysed after stratifying patients into tertiles of baseline ERI. The median CRP level in the highest ERI tertile (9.8 [4.2–22] mg/L) was significantly higher than the median CRP levels in the middle (5.6 [1.7–11] mg/L) and lower (5.7 [2.2–15] mg/L) tertiles (P < 0.01 in both cases). There was no difference in the median CRP levels between the lower and middle ERI tertiles (P = 0.35). When patients were divided into study groups within each of the three tertiles, the
CRP levels did not differ between the study groups at baseline or 12 months, nor when the baseline and 12-month levels were compared within study groups, in any of the tertiles as shown in Table 4. There was no correlation between the change in ERI and change in CRP levels ($r_s = 0.10, P = 0.15$).

**DISCUSSION**

Our results suggest that VE-coated polysulfone membranes do not reduce ERI when compared with directly equivalent high-performance membranes at the study population level. However, we observed a small but significant beneficial effect of the membrane for those patients with the highest ESA resistance at baseline.

Panichi et al. [18] demonstrated reductions in ERI, CRP and interleukin (IL)-6 levels after 6 month dialysis treatment with low-flux VE-bonded membranes. In a smaller study, Mandolfo et al. [16] similarly reported a reduction in ERI after 6 months for patients with central venous catheters dialysing with a VE-bonded membrane. The data from the present study appear to contradict these two studies; however, there were differences in study design. The control and VE membranes in the Panichi et al. [18] study were both low-flux, although previous studies have not demonstrated an effect of membrane flux on anaemia [26–29] or inflammation [29–31]. The Mandolfo et al. [16] study enrolled only patients dialysing via catheters; few of our patients used CVCs as their access. In line with the findings of the present study, two previous randomized controlled trials have similarly reported no benefit of VE-bonded polysulfone membranes on ERI at the study population level [19, 21]. The pilot study by Andrulli et al. [19] only enrolled 19 patients and was therefore underpowered to demonstrate a difference. The larger VEESA study [21] reported 12-month data on 213 patients; however, the factorial design stratifying patients on the basis of their starting haemoglobin level and the failure to report absolute ERI levels makes direct comparisons with the present study impossible.

The ERI levels at baseline, both here and in the other published study reporting absolute ERI levels and showing no ESA-sparing effect of a VE-membrane [19], were lower than the studies demonstrating a significant benefit [16, 18]. The UK Renal Registry reports conducted immediately before [24] and during [25] the study period suggested that our HD population had among the lowest levels of ESA resistance in the UK; these findings prompted our post hoc analyses. The tertiles with the highest ERI were comparable with patients in the studies that produced positive outcomes [16, 18]. It is therefore possible that the VE membranes have an ESA-sparing utility in patients with increased levels of ESA resistance. Whilst this is an interesting observation, it should be noted that our study was powered to look for changes at the whole population level, and the comparatively small size of the subgroup means that this hypothesis requires further testing.

Patients in the highest tertile of ERI had significantly higher CRP levels. However the reduction in ERI for those patients dialysing with the VE membranes was not mirrored by reductions in the CRP levels, and the change in ERI and CRP levels after 12 months was not correlated. This suggests that the reduction in ESA resistance seen in the high ERI group was not due to a reduction in systemic inflammation. Panichi et al. [18] reported improvements in both ERI and markers of inflammation after 6 month dialysis treatment with VE-bonded membranes and similarly observed that the changes in these parameters were not correlated. Taken together, these suggest that improvements in ERI, where apparent, may not be related to the anti-inflammatory effects of VE.

The present study represents the largest prospective randomized controlled trial examining the ESA-sparing potential of VE-bonded polysulfone dialysis membranes to date. Overall, no significant improvements in ESA resistance were observed. However, our data and that of others [16, 18] suggest VE-bonded membranes may improve ESA-responsiveness in ESA-resistant individuals.

**SUPPLEMENTARY DATA**

Supplementary data are available online at [http://ndt.oxfordjournals.org](http://ndt.oxfordjournals.org).
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CONFLICT OF INTEREST STATEMENT

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