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ORIGINAL ARTICLE

Prospective randomized pilot study on the effects of two synthetic high-flux dialyzers on dialysis patient anemia

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ABSTRACT

Purpose: *Anemia in chronic kidney disease dialysis patients is a complex syndrome involving many causes. Adequate dialysis can contribute to its correction through many mechanisms, including the removal of molecules that may inhibit erythropoiesis. The aim of this pilot study was to evaluate the effect on renal anemia of two synthetic, high-flux dialyzers (polynephron vs. high-flux polysulphone).*

Methods: *20 dialysis patients (11 male; mean age: 72 years) were randomly assigned and studied for 6 months. There were 2 dropouts in each group. Each patient underwent 3 hemodialysis treatments per week without any difference in dialysis prescription. At T = 0 and T = 6 (after 6 months), instantaneous plasma clearances and reduction rates of small solutes, β2-microglobulin protein (β2-μ); hemoglobin (Hb), and iron pattern were measured. The effect on anemia was evaluated by calculating the Erythropoesis Stimulating Agent (ESA) doses and the Erythropoietin Resistance Index (ERI).*

Results: *Kt/V increased between T0 and T6 in both groups. β2-μ pre-dialysis levels significantly decreased between T0 and T6 in both dialyzer groups ($p<0.001$ in both groups). The Hb levels increased between T0 and T6, but significantly only for the polynephron patient group ($p = 0.006$ and 0.142). ESA dose did not change significantly. The ERI decreased by 22.7% between T0 and T6 in the polynephron-group and increased by 14% in the others; these changes were not significant.*

Conclusions: *High-flux filters improved Hb levels, although only significantly in the polynephron group, suggesting a possible different effect. The results should be interpreted with caution and tested in an appropriately powered, large, prospective, randomized control trial.*

KEY WORDS: *High-flux dialysis, Anemia, EPO resistance, ESA, Kt/V*

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INTRODUCTION

Anemia represents a major clinical problem in patients with chronic kidney disease stage 5 on dialysis (CKD 5 D) and, together with hypertension, causes hypertrophy and subsequent cardiac dilation. Given that in these patients cardiovascular disease is the major cause of morbidity and mortality, great effort should be made to prevent, reverse, or at least reduce this complication.

Over the last 20 years, the availability of erythropoiesis stimulating agents (ESAs) has led to the almost complete disappearance of severe anemia associated with CKD requiring repeated blood transfusions. Unfortunately, response to ESAs depends on several factors, including iron status, inflammation, dialysis adequacy, hyperparathyroidism, and baseline hemoglobin (Hb) levels. Thus a number of patients fail to achieve the Hb target range recommended by international guidelines (1, 2). The term recombinant human erythropoietin (rhEPO) resistance is used to define patients that fail to achieve their Hb target, despite an increased ESA dose. The ESA resistance index is a composite variable based on the ESA dose (numerator) and patient's response in terms of Hb levels (denominator).

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Recently, it has been suggested that there are possible negative effects from high ESA doses, which has caused concern among nephrologists. Consequently, using the lowest possible ESA doses in correcting anemia of CKD patients is at present considered an important goal (3).
It has recently been found (4) that ESA hyporesponsiveness could also be related to oxidative stress, which is increased in hemodialysis patients not only because of their uremic status per se, but also because of hemodialysis-related factors including biocompatibility and flux of dialysis membranes, and the chemical and biological quality of the water and dialysate. As medium-large molecular-weight inhibitors can be removed only by more permeable membranes, convective treatments could theoretically improve anemia correction by a higher removal of medium and large solutes (possibly containing bone marrow inhibitors). High-quality water and dialysate – from the microbiological and pyrogenic points of view – used with convective treatments could also play an important role.
The aim of this pilot study was to evaluate the effect of two high-flux membranes: the polysulphone membrane Fresenius HF80s (referred to as PS, 1.80 m^2; Fresenius, Bad Homburg, Germany), and the polynephron membrane Nipro ELISIOTM-190H dialyzer (referred to as PN; Nipro Europe, Zaventem Belgium;1.9 m^2), on anemia status and the ESA resistance index in stable hemodialysis patients.

PATIENTS AND METHODS

This was a 6-month prospective, randomized, parallel control study.
Patients of both genders aged >18 years were considered eligible for the study, if they were receiving standard bicarbonate hemodialysis with low-flux dialyzer treatment for at least 6 months; and stable ESA and iron therapies for at least 3 months, with adequate iron stores (ferritin levels >200 ng/ml and transferring saturation >20%). Exclusion criteria were congenital hemoglobinopathies and malignancies; as well as infection, vascular access thrombosis, cardiovascular disease, hemorrhages, major surgery, and blood transfusion in the previous 3 months.
The local ethics committee approved the study; patients gave their written informed consent and were randomly assigned to the high-flux polysulphone (PS group) or the high-flux polynephron (PN group).

Clinical data

The dialyzer was randomly assigned with a 1:1 ratio at the beginning of the study, using a four-block randomization with sealed envelopes. Pre- and post-dialysis body weight, blood pressure, and heart rate were recorded at baseline and every month. All drugs administered during dialysis session were recorded, as were all the prescribed inter-dialysis therapies.

Hematological data

Pre-dialysis Hb and hematocrit (Ht) levels were recorded every month, while instantaneous plasma clearances (K) and reduction rates (RR) of small solutes (urea, creatinine, phosphate), and medium molecular weight (MMW) protein (β2-μ), 11,800 Da; serum Iron, TIBC, ferritin were measured at T = 0 and T = 6. The normalized protein catabolic rate was calculated according to the equation proposed by Depner et al (5) and using the equilibrated Kt/V value. Parathyroid hormone (PTH) levels were also recorded.

Main response variable

The main outcome variable was the ESA resistance index, a combined variable calculated by dividing the weekly ESA dose (UI) by the product of Hb level (g/dl) and end-dialysis body weight (kg).

Sample size

Considering the pilot nature of the study, a sample size of 20 patients (10 per group) was considered sufficient to provide reasonable control over random variations in the ESA resistance.

Statistical analysis

Data were described using mean values ± standard deviation (SD). The between-group differences were assessed by means of the Student's *t*-test for paired data, comparing the within-group comparisons of baseline data with the data after 6 months. A p value of <0.05 was considered significant.

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RESULTS

Baseline data

Twenty patients on standard bicarbonate hemodialysis with a low-flux dialyzer were enrolled and randomly assigned to the PN treatment (n = 10) or PS treatment (n = 10); none was diabetic. One patient per group died during the follow-up because of infectious diseases. Another patient per group was hospitalized and changed type of dialysis membrane due to organizational problems. Sixteen patients were fully analyzed. Their baseline characteristics are reported in Table I. The patients had undergone hemodialysis three times per week for a median of 43.5 months (PN group) and 51 months (PS group) (p = 0.86), with a mean dialysis duration of 243.8 ± 10.6 and 236.3 ± 29.7 minutes in the PN and PS groups, respectively; the difference was not significant (p = 0.86). All twenty patients received ESAs (75% were treated with darbepoetin, 20% with epoetin alpha and 5% with epoetin beta); the dosage of ESA in patients treated with darbepoetin was converted from mcg to IU multiplying *200; the mean dose was 74.4 ± 83.7 IU/kg per week i.v. in the PN group and 60.6 ± 36.2 IU/kg per week i.v. in the PS group, with no difference between the groups (p = 0.73). The mean Hb levels were 11.2 g/dl and 11.4 g/dl in the PN group and PS group, respectively, and there was no between-group difference (p = 0.49). The variables related to iron stores (transferrin saturation and ferritin levels) were also within the desired levels, without any significant differences between the two groups (Tab. I). All patients received intravenous iron (mean dosage 44.9 ± 35.9 mg/week in PN group and 41 ± 62.5 mg/week in PS group, p = 0.86). The mean ESA resistance index was 6.4 ± 6.7 IU/kg *g of Hb/week in PN group and 5.3 ± 2.9 IU/kg *g of Hb/week in PS group, with no between-group difference (p = 0.72). Equilibrated Kt/V and the normalized protein catabolic rate were 1.47 ± 0.2 and 0.96 ± 0.2 g/kg per day in PN patients and 1.49 ± 0.3 and 0.94 ± 0.2 g/kg per day in PS patients, with no between-group differences (p = 0.87 and p = 0.75, respectively). The mean level of high-sensitivity CRP was not significantly different between the PS and PN groups: 1.1 ± 0.9 mg/dl and 0.9 ± 0.8 mg/dl, p = 0.67. β2-μ plasma levels were significantly lower in the PN group (28.0 ± 9.1 vs. 41.5 ± 62.5, p = 0.017). Also, PTH and phosphate levels were not significantly different in the two groups.

Follow-up data

Kt/V increased from T0 to T6 (after 6 months) in both groups but the increase was not significant; the normalized protein catabolic rate did not change during the follow-up (data not shown).

PTH levels remain stable at the follow-up and there were no significant differences between the two groups (PN: 248.7 ± 177.4 pg/ml; PS: 287.5 ± 215.9 pg/ml; p = 0.72).

TABLE I - PATIENTS BASELINE CHARACTERISTICS

	PN (n = 8) mean ± SD	PS (n = 8) mean ± SD	*T*-test (*P*)
Age (yrs)	73 ± 8	71 ± 10	0.28
Ferritin (ng/ml)	579.6 ± 467.1	644.4 ± 270.6	0.68
Transferrin sat (%)	36.1 ± 15.7	30.7 ± 7.4	0.41
Hb (g/dl)	11.2 ± 0.7	11.4 ± 0.9	0.49
Ht (%)	34.2 ± 2.8	34.9 ± 2.6	0.47
Albumin (g/dl)	3.6 ± 0.3	3.4 ± 0.3	0.46
hs CRP (mg/dl)	1.1 ± 0.9	0.9 ± 0.8	0.67
P (mmol/l)	1.6 ± 0.5	1.4 ± 0.3	0.45
PTH (pg/ml)	299.9 ± 290.6	291.5 ± 200.9	0.95
β2-μ (ng/ml)	28.0 ± 9.1	41.5 ± 62.5	0.017*
ESA dose (IU/Kkg per week)	74.4 ± 83.7	60.6 ± 36.2	0.73

Hb = Hemoglobin; Ht = Hematocrit; hs CRP = high sensibility C-reactive protein; P = phosphate; PTH = Parathyroid hormone; β2-μ = β2-Microglobulin.

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TABLE II - β2-MICROGLOBULIN PRE-DIALYSIS LEVELS (ng/ml)

	PS (n = 7)	PN (n = 8)	Difference	*P*
T0	42.6 ± 17.7	28.0 ± 9.1	14.6 ± 7.1	0.061
T6	12.7 ± 6.6	9.9 ± 4.8	2.8 ± 2.95	0.36
Difference	29.9 ± 7.14 (-70.2%)	18.1 ± 3.61 (-64.6%)	11.8 ± 2.9	0.001*
P	0.001*	0.0000*		

PS = polysulphone; PN = polynephron.

TABLE III - HEMOGLOBIN LEVELS (g/dl)

	PS (n = 8)	PN (n = 8)	Difference	*P*
T0	11.4 ± 0.9	11.2 ± 0.7	0.2 ± 0.4	0.627
T6	12.1 ± 0.9	12.5 ± 0.9	0.4 ± 0.4	0.389
Difference	0.7 ± 0.45 (+6.1%)	1.3 ± 0.4 (+11.6%)		0.388
P	0.142	0.006*		

PS = polysulphone; PN = polynephron.

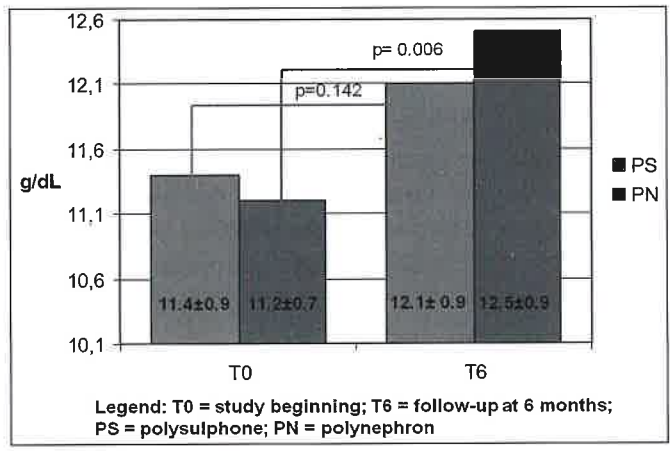

Fig. 1 - *Hemoglobin level changes during the study follow-up.*

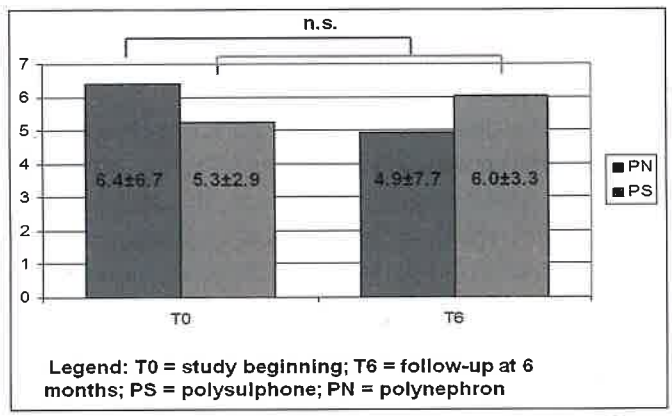

Fig. 2 - *ESA resistance index changes during study follow-up.*

Despite the baseline imbalance, there was a significant reduction in β2-μ pre-dialysis levels between T0 and T6 in both dialyzer groups, without any difference between the two groups (data reported in Tab. II).

The Hb levels increased from T0 to T6 (Tab. III and Fig.1), this increase was significant (p = 0.006) only for the PN group. The increase in Hb level was not significantly different between the two groups.

The ESA and iron treatment did not change significantly during the 6-month period. The ERI decreased by 22.7% between T0 and T6 in the PN group and increased by 14% in the PS group, but these changes were not statistically significant (Fig. 2). The difference in the changes of the ERI in the two groups was not significant.

DISCUSSION

Partial correction of anemia in dialysis patients is an important goal, considering that severe anemia is responsible for many comorbidities and reduces patient quality of life. Iron and ESA therapies are of paramount importance in correcting CKD patient anemia, and ESA availability dramatically improves the quality of life in dialysis patients. Unfortunately, hyporesponsiveness to ESA treatment is a growing problem due to the characteristics of today's dialysis patient population. Thus, large doses of ESAs are often necessary to reach the suggested hemoglobin target range (3). This fact not only increases the cost of the treatment but is also very often inefficient and is associated with increased morbidity and mortality in dialysis patients as well (6). Thus, minimizing ESA doses is increasingly recognized as an important aim.

In dialysis patients, the quality of dialysis treatment is an important factor in correcting anemia in this patient population. Thus, adequate Kt/V is considered of paramount importance for reaching this goal (7). However, it was soon recognized that the quality of the biocompatible high-flux membranes is just as important as the quality of the water,

based on the ability of these membranes to remove medium and large solutes, possibly inhibiting bone marrow. Many studies (8, 9), although not all (10, 11), accordingly reported better correction of anemia and/or a sparing of ESA doses in convective treatments (high-flux dialysis, hemofiltration, and hemodiafiltration). For these reasons, improving the quality of the dialysis filter used in these techniques could further decrease the oxidative stress related to blood–membrane contact and better remove potential hemopoiesis inhibitors.

In this study we evaluated the effect of two high-flux dialyzers, the PN Elisio and the PS HF80s, with regard to Hb levels and the ERI in dialysis patients.

Hemoglobin levels increased in both groups, although this increase was statistically significant only in patients treated with PN. There were no significant differences in ESA and iron doses or in iron store indexes between the two groups. There was a non-significant increase in Kt/V in both groups and no difference between the two groups.

Baseline β2-μ plasma levels were significantly lower in the PN group compared with the PS group. This was most likely due to the variables random distribution. The starting imbalance was not maintained at the follow-up.There was a significant reduction in β2-μ levels in both groups, underlining the efficacy of the two dialyzers in removing medium-size molecules. This difference seems higher on the PS patient group, although not significantly, and β2-μ plasma levels were very similar in the two groups at the end of the observation period (see Tab. II). It is well known that β2-μ levels could be related to chronic inflammation. Even if PCR levels were not significantly different in the two study groups at the beginning of the observation period, baseline β2-μ plasma levels could influence the ESA response in the PN and PS patients, with an increase in Hb levels in PN group.

Instead, the different effect on Hb levels does not seem to be related to a better removal of low or medium molecule toxins, possibly impairing the ability of bone marrow in producing red blood cells.

It is well known that uncontrolled hyperparathyroidism causes bone marrow fibrosis, leading to erythropoietin (EPO) resistance (12). In this study, PTH levels were not significantly different in the two groups at baseline as well as at the end of follow-up, so it is impossible to evaluate the effect of calcium-phosphorous metabolism on Hb levels in our population.

Strangely enough, given that with both filters there was an increase of the Hb levels, the ERI did not change significantly in the two filter groups. However, the pilot nature of the study design of this trial, without a sample size calculation, should be taken into consideration in interpreting these results, because, by definition, a second type statistical error is very frequent in pilot studies. This is the reason why a formal statistical analysis is not suggested for these studies.

In conclusion, the results of this prospective, randomized pilot study further suggest the ability of high-flux membranes to improve the Hb levels of dialysis patients. The fact that the increase in the Hb level was only significant in patients treated with PN suggests a possible different effect even between high-flux filters, although, considering the pilot nature of the study design, these results should be interpreted with caution and tested in a large prospective, appropriately powered, randomized control trial.

Conflict of Interest Statement: The dialyzers for this study were kindly provided by Nipro Europe, Zaventem, Belgium, who agreed to the publication of the study results. The authors declare that they have no conflict of interest in this research.

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