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Long Dialysis Time is the More Important Factor of Erythropoietin Response in Hemodialysis Patients with Diabetes than Kt/V

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Abstract

Background: Though inadequate dialysis is a known risk factor for resistance to erythropoietin (EPO) therapy, there is no consensus about the relationship between hemodialysis (HD) time and EPO requirement. Our study sought to explore the relationship between EPO dosage and dialysis time in HD patients with diabetes.

Methods: We report a cross-sectional analysis of the relationship between EPO dosage and dialysis time in HD patients with diabetes. A total of 77 patients with diabetes receiving maintenance HD at three outpatient HD facilities in Japan were included. At one such facility, HD time was 6 hours (n=37), and at the other facilities, HD time was 4 hours (n=40). In 6-hour HD patients and 4-hour HD patients, we studied parameters of weekly EPO requirement, Kt/V, hemoglobin, ferritin, albumin, C-reactive protein and intact parathyroid hormone. These parameters were analyzed with JMP9™ statistical software (SAS Institute).

Results: Means for hemoglobin, ferritin, albumin, C-reactive protein and intact parathyroid hormone were not significantly different between the 6-hour and 4-hour HD patient groups. The EPO requirement was significantly lower among 6-hour HD patients (3111.8 ± 2360.8 versus 5682.9 ± 3863.3 U/week. P=0.0007). Kt/V was not significantly different between the two groups.

Multiple regression analysis with EPO requirement as the dependent variable showed that dialysis time was the only significant independent variable (P=0.0001).

Conclusions: Six-hour HD without a significant increase in dialysis dose, as judged by Kt/V, can reduce the dose of EPO in HD patients with diabetes.

Keywords: Erythropoietin requirement; Hemodialysis time; Kt/V; Inadequate dialysis; Long hemodialysis; Membrane surface area; 6 hour-hemodialysis

Introduction

Renal anemia is a very frequent problem that affects hemodialysis (HD) patients. The main pathogenic factor is a reduction in erythropoiesis caused by reduced renal production of erythropoietin (EPO) and by resistance of bone marrow cells to this hormone.

Before the 1990s, anemic HD patients were submitted to inefficient treatment by blood transfusions and administration of androgenic-anabolic steroids. The introduction of recombinant human EPO therapy has improved quality of life for HD patients with severe anemia and made it possible to control anemia in attempts to achieve normal hemoglobin (Hb) target.

Randomized trials have shown increased mortality [1] or no beneficial clinical effects [2] among those assigned to normal Hb targets. High doses of EPO increase the risk of death and cardiovascular events in HD patients [3-5]. Given these findings, it is important to explore the factors of Hb response to EPO.

Although some studies have proved that iron deficiency [6-10], inflammatory disorders [11,12], hyperparathyroidism [13,14], malnutrition [15-17] and a low standardized HD dose of urea [18-22] increase the EPO requirement, little actual study has been done to explore the relationship between dialysis time and EPO requirement. Our study was undertaken to test the a hypothesis that longer HD time can reduce the EPO requirement in HD patients.

Methods

We conducted a cross-sectional study on a total of 77 diabetes patients receiving maintenance HD for 7-240 months (median 62.4 months). Subjects were recruited from three outpatient HD facilities in Japan. At one facility, dialysis time was 6 hours (n=37), and at the other two facilities, dialysis time was 4 hours (n=40).

Included patients were age 20 years or older and had undergone maintenance HD three times a week for at least six months as treatment for end-stage renal disease due to type 2 diabetes mellitus. Patients with any blood loss, blood transfusions, hospitalizations, or infections occurring within six months preceding the study were excluded.

Conventional dialysis was performed with the use of high-flux dialysis membranes and bicarbonate-based dialysate. All patients received EPO and an iron preparation intravenously.

In 6-hour and 4-hour HD patients, we studied parameters of weekly EPO requirement, Kt/V, membrane surface area, quantity of blood flow (QB), quantity of dialysate flow (QD), age, length of treatment,

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sex, body mass index (BMI), height, dry weight (DW), Hb, ferritin, albumin (Alb), C-reactive protein (CRP) and intact parathyroid hormone (i-PTH). All data are expressed as mean ± SD. Statistics were evaluated by regression analysis, Student's t-test for unpaired data, and multiple regression analysis. Significant differences were defined as $p<0.05$. Parameters were analyzed with JMP9™ statistical software (SAS Institute).

Results

Table 1 shows a comparison in 4-hour HD patients and 6-hour HD patients between weekly EPO requirement and Kt/V, membrane surface area, QB, QD, age, length of treatment, sex, BMI, height, DW, Hb, ferritin, Alb, CRP and i-PTH.

The EPO requirement was significantly lower in 6-hour HD patients (3111.8 ± 2360.8 versus 5682.9 ± 3863.3 U/week. P=0.0007). Membrane surface area was significantly smaller in 6-hour HD patients (1.1 ± 0.2 versus 1.6 ± 0.4 m^2, P<0.0001), and Kt/V was not significantly different between the two groups. Kt/V, QB, QD, age, length of treatment, sex, BMI, height, DW, Hb, ferritin, Alb, CRP, and i-PTH did not differ between the two groups.

Table 2 shows multiple regression analysis results for all patients, with EPO dosage as a dependent variable. Dialysis time was the only significant factor (r^2=0.25. P=0.0001). Age, Kt/V, CRP, and ferritin were not significant factors.

Discussion

The major new finding of the present study is that long HD without a significant increase in dialysis dosage, as judged by Kt/V, may reduce EPO dosage in HD patients.

	4-hour HD, n = 40	6-hour HD, n = 37	p value
Epoetin dose (U/week)	5682.9 ± 3863.3	3111.8 ± 2360.8	<0.0007
Kt/V	1.4 ± 0.2	1.4 ± 0.2	NS
Membrane surface area (m^2)	1.6 ± 0.4	1.1 ± 0.2	<0.0001
Quantity of blood flow (mL/minute)	199.1 ± 23.3	188.4 ± 20.6	NS
Quantity of dialysate flow (mL/minute)	485.6 ± 13.5	500.0 ± 0.0	NS
Age (years)	65.4 ± 11.7	67.2 ± 9.2	NS
Length of treatment (years)	5.3 ± 4.2	5.0 ± 4.2	NS
Male (%)	62.5	64.9	NS
Body mass index	21.4 ± 3.7	21.5 ± 3.1	NS
Height (cm)	158.6 ± 8.5	161.1 ± 10.2	NS
Dry weight (kg)	54.0 ± 10.8	55.8 ± 10.2	NS
Hemoglobin (g/dL)	11.1 ± 1.1	11.0 ± 0.9	NS
Ferritin (ng/mL)	175.9 ± 118.7	172.0 ± 88.6	NS
Albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.4	NS
C-reactive protein (mg/dL)	0.5 ± 0.7	0.4 ± 0.5	NS
Intact parathyroid hormone (ng/mL)	137.1 ± 108.8	114.3 ± 122.3	NS

Table 1: Comparison between epoetin dose, Kt/V, membrane surface area and other parameters in 4-hour HD and 6-hour HD.

	Coefficient	Standard error	t statistic	p value
Age	13.78	31.02	0.44	0.66
Dialysis time	-1248.63	310.15	-4.03	0.0001
Kt/V	1298.04	1573.96	0.82	0.41
C-reactive protein	428.90	522.17	0.82	0.41
Ferritin	3.44	1.92	1.79	0.08

Table 2: Multiple regression analysis with weekly epoetin dose as dependent variable.

Movilli et al. reported a negative relationship between EPO dose and Kt/V [15,16].

Gawada et al. also reported that EPO response was high at Kt/V of 1.4 or higher [17]. However, these studies did not investigate the association between dialysis time and EPO requirement.

At the dialysis center in Tassin, France, 59 patients with 8-hour HD were compared with 53 patients with 3- to 5-hour HD and EPO requirement was lower in 8-hour HD patients than those in 3- to 5-hour HD patients [18]. However, Kt/V was also higher in the 8-hour HD patients than 3- to 5-hour HD patients (1.93 and 1.55-1.58, respectively).

In the present study, we found the lower EPO requirement among 6-hour HD patients despite a lack of difference in KtV, and the fact that dialysis time was the only significant factor even in multiple regression analysis. Thus dialysis time itself may be a crucial factor improving response to EPO.

In turn, we attribute the lack of difference in Kt/V between 6-hour and 4-hour HD patients to a significantly smaller membrane surface area in 6-hour HD patients. Since the opening of the 6-hour HD facility in 1989, all HD patients there have undergone 6-hour HD using a dialyzer with a small membrane surface area (1.1 ± 0.2), and Kt/V is also by no means high (1.6 ± 0.4). Notwithstanding, results have been extremely good, with 5-year survival for HD patients at 81.9%, 10-year survival at 55.3%, and 15-year survival at 42.5%. Similar, good results have also been obtained among HD patients with diabetes, with 5-year survival at 79.7%, 10-year survival at 47.9%, and 15-year survival at 21.0% [19].

Although some studies have proved that the iron deficiency [5-7], inflammatory disorders [8,9], hyperparathyroidism [10,11], and malnutrition [12,13] increase the EPO requirement, our study found no significant differences among subject groups in ferritin, CRP, i-PTH, and Alb.

High doses of EPO increase the risk of death and cardiovascular events in HD patients [3,4]. Even though we cannot conclude that the mortality risk is due to EPO toxicity, HD patients using high dosages of EPO must be seen as high-risk cases. Long HD is known to have a good survival prognosis [19-23], one factor of which may be the low EPO requirement. EPO is also an extremely high-cost drug, and the reduced EPO requirement in long HD also has an economic benefit.

Values of Kt/V do not reflect medium-large molecular weight substances and other aspects of dialysis dosage and can also provide a good result if V is low due to malnutrition; consequently, care is needed when using this index as a dialysis dosage parameter [24,25].

Our study is a cross-sectional analysis among subjects of HD patients with diabetes, which must be followed by a prospective randomized analysis among subjects comprising all HD patients. The detailed pathophysiology whereby long HD reduces EPO requirement is also unclear and further basic research is needed.

In conclusion, our study shows that dialysis time rather than Kt/V is the most important factor of EPO response in HD patients with diabetes.

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