

Registry Report

Factors influencing anaemia in dialysis patients. A special survey by the EDTA-ERA Registry

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countries as did the transfusion policy. In view of the high costs of the rHuEpo treatment and potential side-effects, factors such as method of dialysis and hours of haemodialysis per week should be taken into consideration in the treatment of anaemia in dialysis patients.

Key words: anaemia; sample study; EDTA Registry; dialysis patients; recombinant human erythropoietin (rHuEpo)

Introduction

The degree of anaemia in progressive renal failure increases as the glomerular filtration rate declines [1] and in patients treated by either haemodialysis or peritoneal dialysis, anaemia is almost invariably present. Diminished erythropoietin production seems to be the important pathogenetic factor, although other factors such as circulating inhibitors of erythropoiesis and decreased red cell survival have been described. Anaemia contributes considerably to morbidity and impairs the quality of life in patients on dialysis, and the introduction of rHuEpo was a major breakthrough in the management of patients with end-stage renal disease [2,3].

Data concerning the influence of dialysis itself on the prevailing anaemia are conflicting [4,5]. A time-related increase in haematocrit on maintenance haemodialysis has been described and in some cases has been associated with concurrent acute or chronic hepatitis [6,7]. It has often been suggested that acquired renal cysts may be responsible for an increase in haematocrit, but recently this correlation has been questioned [8–10].

To investigate transfusion dependency and the influence of several variables on anaemia in a large group of dialysis patients the EDTA Registry designed a special study concerning patients dialysed throughout 1987. In that particular year prescription of rHuEpo had barely started, and only a few patients in a minority of centres were receiving the drug. Hence there were no confounding effects of rHuEpo treatment. The database of the EDTA Registry made it possible to combine the results obtained in a special questionnaire with the extensive patient data already available from the Registry's file.

Abstract. The European Dialysis and Transplantation Association—European Renal Association (EDTA-ERA) Registry conducted a special study on anaemia in dialysis patients because it seemed important to elucidate the various factors that influence the degree of anaemia and the use of regular transfusions in dialysis patients before the introduction of recombinant human erythropoietin (rHuEpo) for larger groups of patients. In a 20% sample of all patients recorded to have been dialysed throughout 1987, statistically significant associations could be found by multifactorial analysis between haemoglobin (Hb) concentration and age, sex, primary renal disease, type of treatment, hours of dialysis per week, and number of years on renal replacement therapy. The type of dialyser membrane did not seem to play a role (although there was weak evidence of an effect of the dialyser). Mean Hb concentration for dialysis patients differed between

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Subjects and methods

At the end of 1987 there were 65 200 patients on the Registry who were alive and had been treated throughout the year 1987 by dialysis (centre haemodialysis, home haemodialysis, intermittent peritoneal dialysis, or CAPD). Patients were sorted into random order within each centre in each country. After sorting, a 20% sample was taken, resulting in 13 040 patients selected. Each centre was sent a questionnaire with the name or initials of the randomly selected patients. The doctors responsible for these centres were asked to record the Hb concentration in December 1987. In addition they had to indicate for each patient the need of regular transfusion (defined as more than 1 unit of blood per 2-month interval). Information was also requested regarding bilateral nephrectomy and treatment with rHuEpo in 1987 and/or in 1988. Routine software tools made it possible to link the data from the special questionnaire with the other patient data already available on the Registry's file.

Of the special questionnaires concerning 13 040 patients mailed in January 1989, 8625 were returned by the end of 1989. Of these, 7948 patients had Hb values recorded (92.2%) whilst 565 (6.6%) patients had to be excluded because of uncertainty regarding the absence of any changes in method of RRT during 1987, and another 515 (6%) because they had undergone bilateral nephrectomy or had been treated with rHuEpo in 1987. This left 6869 (79.6%) patients for analysis.

Data on type of dialyser most frequently used during 1987 for each individual, including the type of membrane and its ultrafiltration characteristics, were available for 4591 patients on haemodialysis. The variables listed in Table 1 were analysed by multiple regression against Hb concentration at 31 December 1987 and by logistic regression [11] against the need for transfusion during 1987.

The multifactorial analyses were carried out using the statistical package GLIM [12].

Results

Validation of the sampling procedure

Primary renal disease was selected as the profile characteristic to test the validity of the sampling procedure. In Figure 1 the distribution of primary renal disease in patients sampled can be compared to the distribution in all patients eligible for the sample. That primary renal diseases are similarly distributed in both groups

Table 1. Variables studied in the multifactorial regression analyses

Country of treatment
Sex
Age
Primary renal disease
Type of initial treatment
Type of most recent treatment
Length of time since start of treatment
Length of time on most recent treatment
Need for regular transfusions
Number of dialysis sessions per week
Hours of dialysis per week
Membrane type of dialyser
Ultrafiltration characteristics of the dialyser

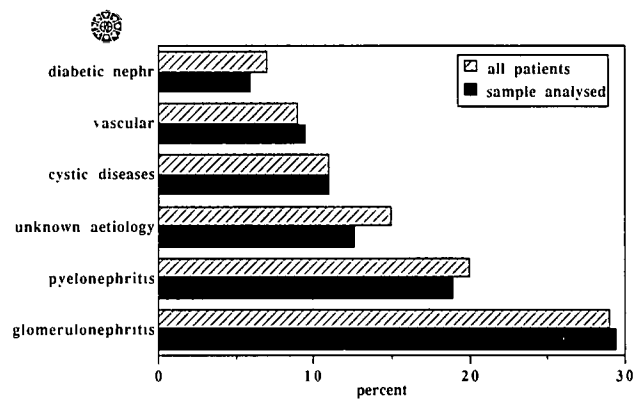


Fig. 1. Proportional distribution of different renal diseases among all patients dialysed throughout 1987 and among 6869 patients entered into the analyses.

of patients indicates that no bias for this factor was created by the sampling procedure.

Countries

In Table 2 the mean Hb concentrations are given according to the countries. A wide range is seen between countries such as the then German Democratic Republic and Czechoslovakia for whom mean Hb concentrations under 80 g/l were recorded, whereas

Table 2. Mean haemoglobin concentration according to country. Countries with less than 10 patients were excluded

	<i>n</i>	Hb (g/dl) Mean \pm SD
Austria	88	83.8 \pm 17.2
Belgium	224	88.4 \pm 16.5
Czechoslovakia	123	78.3 \pm 14.2
Denmark	39	89.4 \pm 19.3
Finland	38	90.7 \pm 21.1
France	1118	91.5 \pm 20.5
Germany (East)	175	78.8 \pm 15.4
Germany (West)	1335	90.5 \pm 19.2
Greece	110	91.9 \pm 18.9
Hungary	58	84.9 \pm 15.9
Ireland	31	83.6 \pm 17.7
Israel	78	85.9 \pm 18.1
Italy	1160	88.4 \pm 19.6
Netherlands	108	87.7 \pm 22.2
Norway	11	90.6 \pm 12.0
Poland	85	87.6 \pm 18.5
Portugal	187	87.6 \pm 20.4
Spain	913	89.0 \pm 21.3
Sweden	83	86.6 \pm 18.7
Switzerland	137	91.8 \pm 22.1
Turkey	24	86.9 \pm 19.3
UK	311	90.8 \pm 21.9
Yugoslavia	253	82.8 \pm 18.2
Luxembourg	12	87.8 \pm 14.6
Bulgaria	77	84.3 \pm 14.9
Cyprus	14	80.4 \pm 16.2
Tunisia	38	87.4 \pm 21.5
Egypt	17	75.4 \pm 17.8
Libya	13	75.3 \pm 16.6
All	6869	88.7 \pm 19.9

France, the then Federal Republic of Germany, Greece, Switzerland, United Kingdom, and Scandinavian countries had mean Hb concentrations over 90 g/l.

Age and sex

Hb values were higher in males on renal replacement therapy (RRT) and tended to increase with age for both sexes (Figure 2). This is also reflected by the transfusion rate: 21% of all females were regularly transfused *versus* 13% of men.

Primary renal disease

The relationship between anaemia and primary renal disease is depicted in Table 3. Patients with polycystic kidney disease (ADPKD) showed significantly higher Hb concentrations. For all the other primary renal diseases no significant differences in haemoglobin concentration were observed. This is confirmed by the fact that regular transfusion was given to only 7% of patients with ADPKD, whereas 32% of patients with hereditary or familial nephropathy other than ADPKD received regular transfusions.

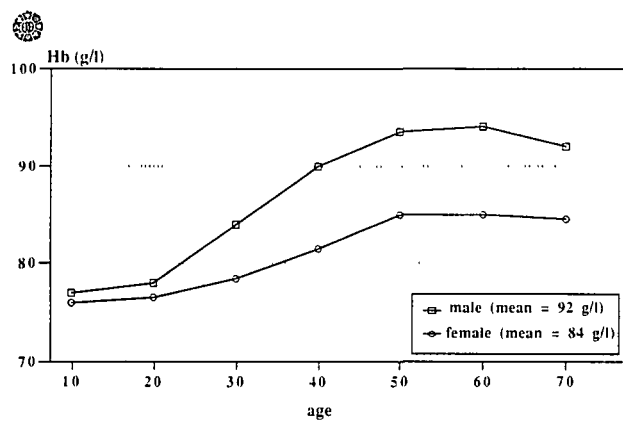


Fig. 2. Mean haemoglobin concentration according to sex and age.

Table 3. Mean haemoglobin concentration for selected primary renal diseases

Primary renal disease	Hb (g/l) Mean ± SD	n
Aetiology uncertain	86.5 ± 18.9	844
Glomerulonephritis	87.6 ± 19.8	1972
Severe nephrotic syndrome in children	78.2 ± 18.8	5
Pyelonephritis/interstitial nephritis	86.1 ± 18.6	1336
Analgesic nephropathy	86.3 ± 17.9	209
Adult polycystic kidney disease	91.6 ± 21.4	603
Diabetic nephropathy	90.2 ± 17.9	424
Renal vascular disease	88.5 ± 17.6	625
Congenital/hereditary renal disease	88.5 ± 22.8	86
All	88.7 ± 19.9	6860

Method of treatment and time spent on renal replacement therapy

In patients for whom CAPD was recorded as the most recent mode of RRT the mean Hb concentration was 96.1 g/l. Home haemodialysis patients displayed haemoglobin concentrations with a mean of 95.1 g/l. For hospital haemodialysis patients the mean Hb concentration was lower at 87.4 g/l, while IPD patients (n = 27) had a mean haemoglobin concentration of 89.9 g/l.

In Table 4 the proportion of patients treated with hospital haemodialysis, home haemodialysis, CAPD, or IPD is shown for four ranges of Hb concentrations, showing that patients with Hb concentrations above 100 g/l were more likely to be on home haemodialysis or CAPD. The same association was found regarding the need for transfusion which was lower in patients on home haemodialysis (9%) and in patients on CAPD (7%) compared with 18% of patients on hospital haemodialysis.

In Figure 3 the influence of length of time on RRT on Hb concentrations and need for transfusion is shown. Both variables were significantly related to time

Table 4. Percentage of patients in four different ranges of Hb concentration according to mode of treatment on 31 December 1987

Hb g/l	< 60	60-79	80-100	> 100	n = 100%
Centre HD	4.0	36.8	36.8	22.4	5804
Home HD	3.2	27.6	32.4	36.8	535
CAPD	1.3	25	34.8	38.8	505

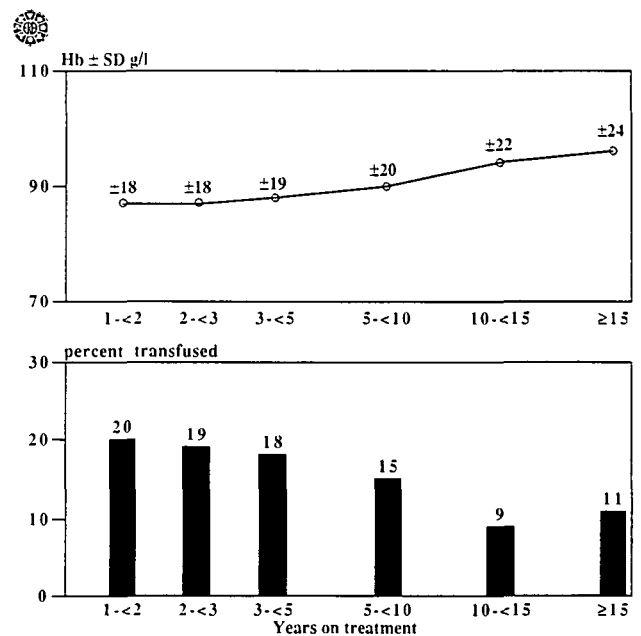


Fig. 3. Mean haemoglobin concentration and percentage of patients needing regular transfusion related to length of time on treatment in years.

on RRT. In a more restricted analysis the influence of time spent on the most recent method of dialysis also showed a positive correlation with Hb concentration. There was a mean increase of 0.74 g/l for every year of treatment for all dialysis modalities combined ($P < 0.001$), although the relationship had a correlation coefficient of only 0.12, indicating the important influence of other parameters.

Haemodialysis schedule and type of dialyser membrane

While patients who were dialysed three times a week had higher haemoglobin concentrations than those dialysed twice a week, and this was also reflected by the need for transfusion (Figure 4), multifactorial analysis disclosed that the variable 'times per week' was itself not significantly correlated with Hb concentration, in contrast to the variable 'number of hours per week'. Hence three-times-weekly dialysis was associated with higher Hb concentrations because these patients were treated for more hours per week than those on twice-weekly dialysis.

The influence of the number of hours dialysis per week is apparent from Figure 5. In this study 11 or more hours of dialysis per week is associated with a steadily increasing Hb concentration. The variables 'mean blood flow/min' or 'dialyser area' were not studied.

To determine the effects of different types of dialysers, patients were grouped according to whether they had been treated most commonly with cellulose as opposed to non-cellulose membranes. This comparison did not yield any difference (mean Hb concentra-

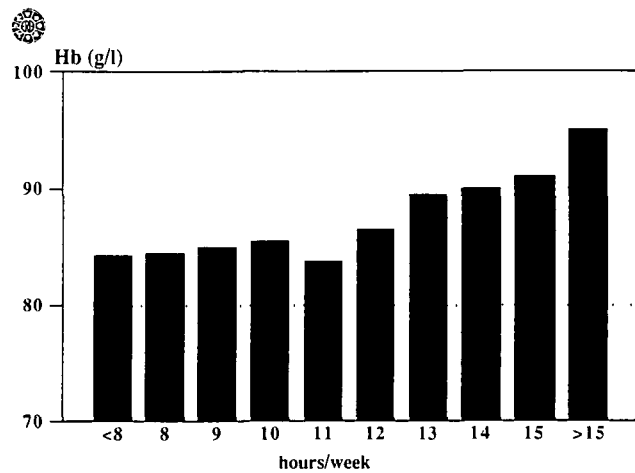


Fig. 5. Mean haemoglobin concentration related to number of hours haemodialysis per week.

tion 88.3 g/l for patients on cellulose versus 88.5 g/l for patients on non-cellulose membranes). In both groups the identical proportion of 17% needed regular transfusions.

A potential effect of porosity of the membrane was tested by grouping patients according to the ultrafiltration capacity of their dialyser. Patients dialysed with low-ultrafiltration dialysers (< 10 ml/h/mmHg TMP) were compared to those with medium ultrafiltration (10–20 ml/h/mmHg TMP) and to those dialysed with high ultrafiltration (> 20 ml/h/mmHg TMP). Again, no significant association was obtained between ultrafiltration capacity and either the haemoglobin concentration ($P = 0.10$) or the need for transfusion ($P > 0.10$).

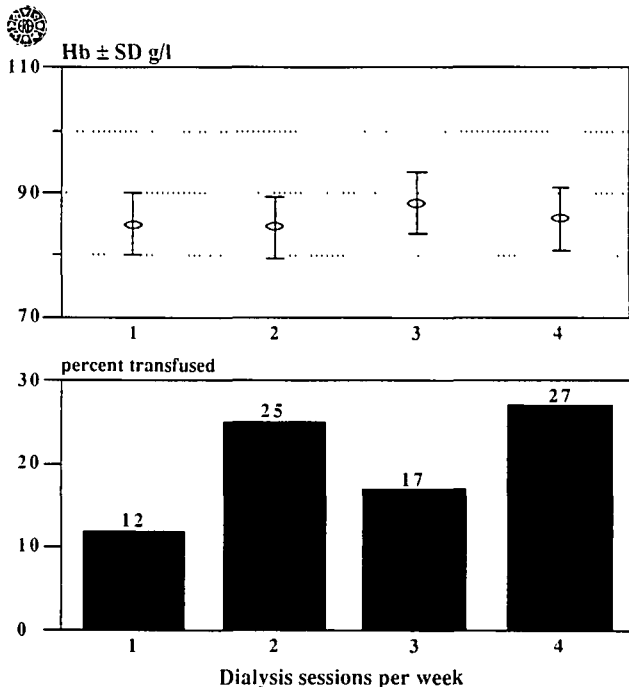


Fig. 4. Mean haemoglobin concentration and percentage of patients needing regular transfusion related to number of dialysis sessions per week.

Discussion

Many factors have been associated with improvement of anaemia in patients undergoing dialysis for end-stage renal disease. A progressive increase in haematocrit has been attributed to improved dialytic technique, to CAPD, to acquired cystic kidney disease, to hepatitis, to parathyroidectomy, and to treatment with androgens [4–10]. The introduction of rHuEpo enabled doctors partially to correct the normochromic normocytic anaemia complicating renal failure [2,3]. The efficacy of erythropoietin treatment is beyond dispute; however, optimizing dialysis treatment may minimize the requirement for the costly drug, allowing a reduction of the dosage needed for correction of renal anaemia.

This study was designed to help fill the gap in our knowledge regarding the influence of various factors on anaemia in dialysis patients using a representative sample drawn from our large database.

Significant associations were found between Hb concentration and primary renal disease, age, sex, type of last recorded treatment, length of time on treatment, number of dialysis sessions per week and hours of dialysis per week (although patients on three-times-

weekly dialysis appeared to have a higher Hb concentration because of the larger number of dialysis hours per week).

The greater Hb concentrations recorded for patients on home haemodialysis and CAPD probably reflect patient selection and freedom from complicating illness. There have been reports that claim a beneficial role of CAPD itself on the anaemia of dialysis patients; an increase in red cell mass is reported by most authors [13,14] whereas a decrease in plasma volume is infrequently reported [13]. There is no evidence for increased erythropoietin secretion in CAPD patients but there may be removal of inhibitors of erythropoiesis [15,16]. Increased red cell longevity is reported in several studies and may also contribute to the lesser degree of anaemia in CAPD patients [14].

The increase of Hb concentration with length of treatment could be explained simply by an increased mortality of the intrinsically less well, and so more anaemic, patients. However, an increase in Hb concentration has also been observed in dialysis patients with liver disease [6,7] and in association with acquired renal cyst formation [8], although the latter mechanism has been disputed [10].

One of the salient findings borne out by this study is the positive correlation between Hb concentration and number of hours spent on haemodialysis per week. That Hb concentration was greater in patients who received more than 12 h dialysis per week implies a role for the amount and the efficacy of dialysis on the degree of anaemia.

In the present study the use of dialysers with non-cellulose membranes and high ultrafiltration capacity was not associated with a higher Hb concentration.

Of all patients evaluated, 16.5% needed regular transfusion, as expected. Among the more anaemic patients with Hb concentrations between 60 and 80 g/l the proportion receiving regular transfusion was 28%, of the less anaemic patients with Hb concentrations between 80 and 100 g/l only 12% were regularly transfused. Transfusion policy may not always have followed strict rules, as financial, political, medical, and religious reasons exist which may inhibit blood transfusion, or even encourage the doctor to transfuse a patient to a higher Hb than his counterparts.

The risks associated with transfusion such as sensitization, transmission of infectious diseases, and possibly transfusion-induced erythroid suppression,

should be weighed against the cost and side-effects of erythropoietin treatment. rHuEpo corrects anaemia in dialysis patients but this study demonstrates that rHuEpo should be used in conjunction with those management options which are themselves correlated with lessening of anaemia and reduced need for regular transfusion.

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