Increasing the Hematocrit Has a Beneficial Effect on Quality of Life and Is Safe in Selected Hemodialysis Patients

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Abstract. Target hematocrit/hemoglobin values in dialysis patients are still controversial. The Spanish Cooperative Renal Patients Quality of Life Study Group (including 34 hemodialysis units) conducted a prospective, 6-mo study of the effect on patient functional status and quality of life of using epoetin to achieve normal hematocrit in hemodialysis patients with anemia. The possible adverse effects of increased hematocrit, patient hospitalization, and epoetin requirements were also studied. The study included 156 patients (age range, 18 to 65 yr). Given the minimal experience in the safety of increasing hematocrit in dialysis patients to normal levels with epoetin, stable patients on hemodialysis who had received epoetin treatment for at least 3 mo and had a stable hemoglobin level of ≥9 g/dl were included in the study. Patients with antecedents of congestive cardiac failure, ischemic cardiopathy, diabetes mellitus, uncontrolled hypertension, cerebrovascular accident or seizures, malfunction of the vascular access or severe comorbidity (defined by a comorbidity index), and those over 65 yr of age were excluded from the study. Quality of life was measured with the Sickness Impact Profile (SIP) and Karnofsky scale. Patients completed questionnaires at home at onset and conclusion of the 6-mo study. Mean hematocrit increased from 30.9 to 38.4% and hemoglobin from 10.2 to 12.5 g/dl during the study. Health indicator scores improved significantly: mean Physical Dimension (SIP) from 5.38 to 4.1 ($P < 0.005$); mean Psychosocial Dimension from 9.2 to 7 ($P < 0.001$); mean global SIP from 8.9 to 7.25 ($P < 0.001$); mean Karnofsky scale score from 75.6 to 78.4 ($P < 0.01$). (SIP is scaled so that lower scores represent better functional status, and *vice versa* for the Karnofsky scale). Therefore, functional status and quality of life improved with increased hematocrit. No deaths occurred. Three patients (2%) were censored for hypertension and nine (5.7%) for thrombosis of the vascular access. The cumulative probability of thrombosis of the vascular access was 0.067. The average epoetin dose rose from 93 ± 62 U/kg per wk at onset to 141 ± 80 U/kg per wk at conclusion, a 51% increase. The number of patients hospitalized decreased and hospital lengths of stay were shorter during the study period than in the same patients in the 6-mo period preceding the study ($P < 0.05$). Nine patients (5.7%) had thrombosis of the vascular access. There were no changes in the prevalence of arterial hypertension, but three patients (2%) showed hypertension that was difficult to control. It is concluded that normalization of hematocrit in selected hemodialysis patients, *i.e.*, nondiabetic patients without severe cardiovascular or cerebrovascular comorbidities, improves quality of life and decreases morbidity without significant adverse effects.

Partial correction of end-stage renal disease-related anemia using recombinant human erythropoietin (epoetin) has been shown to improve the health-related quality of life of chronic dialysis patients (1–3). This improvement is closely linked to the hematocrit level reached during epoetin treatment (4–7).

Although there is no agreement about what the target hematocrit should be in these patients, the recommended target hematocrit has increased over time. The most recent recommendation of the National Kidney Foundation-Dialysis Outcomes Quality Initiative Clinical Practice Guidelines for the Treatment of Anemia in Chronic Renal Failure suggests a range of 33 to 36% for hematocrit and 11 to 12 g/dl for hemoglobin level (8). These figures are clearly lower than normal, which raises the question of why we recommend that dialysis patients remain anemic. The main reason for keeping hematocrit/hemoglobin levels below normal is the risk of serious adverse effects (cardiovascular events, hypertension, thrombosis of the vascular access) when hematocrit is normalized. An additional problem with raising hematocrit to normal levels is the increased cost of treatment because of the need for higher epoetin doses and iron requirements.

In a recent study by Besarab *et al.* (9), these authors do not

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recommend the administration of epoetin to raise hematocrit to normal levels in hemodialysis patients with clinically evident congestive heart failure or ischemic heart disease because of high cardiovascular mortality in these patients. A simplistic conclusion that may be drawn from this study is that it is not advisable to normalize hematocrit in any hemodialysis patient.

However, there is evidence that a normal hematocrit has beneficial effects on the well-being of dialysis patients. Several recent studies have examined the effect of normal hematocrit *versus* lower hematocrit on physical function (10–13) and cognitive function (14–16) in hemodialysis patients. In the study by Besarab *et al.* (9) using the SF-36 quality of life instrument, the physical function increased 0.6 points for each percentage point increase in hematocrit.

The present study was designed to examine the effects of normalizing hematocrit/hemoglobin on the functional status and quality of life of hemodialysis patients. Since the safety of increasing hematocrit in dialysis patients to normal levels with epoetin has not been confirmed, patients with diabetes, older than 65 yr of age, with severe cardiovascular or cerebrovascular comorbidities or with severe associated disease were not selected for our study.

Materials and Methods

Study Design

This prospective study was carried out by the Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology with the participation of 34 Spanish hemodialysis units located in different regions of the country. The main objective of the study was to determine whether the use of higher doses of epoetin to increase hematocrit to near normal levels improves functional status and quality of life in stable hemodialysis patients on epoetin treatment. Possible adverse effects related to higher hematocrit or epoetin dose were evaluated, as well as the increase in the required epoetin dose. The need for hospitalization during the study period also was analyzed.

A prospective 6-mo follow-up study was designed. In a selected group of patients previously treated with epoetin, hematocrit/hemoglobin levels were gradually raised with increased doses of epoetin to near normal levels. The quality of life and functional status of patients were evaluated at the beginning of the study and after 6 mo of follow-up. Patients completed questionnaires at home by themselves. The scores obtained on quality-of-life indicators at the beginning of the study were compared to those obtained at the end of the follow-up period.

Patients

The candidates included in the study were stable patients on hemodialysis who had received epoetin treatment for at least 3 mo and had a stable hemoglobin concentration of ≥9 g/dl and hematocrit of ≥28%. Only nondiabetic patients between the ages of 18 and 65 yr were accepted. Criteria for exclusion included diabetes, uncontrolled hypertension, malfunction of the vascular access (hemodialysis blood flow <300 ml/min, high return venous pressure, and/or recirculation >15%), history of stroke, seizures, symptomatic ischemic heart disease or congestive heart failure, and the presence of severe associated disease (Friedman Comorbidity Index >7; see below) or anemia unrelated to chronic renal failure. Patients who received a kidney transplant or experienced complications possibly related to epoetin treatment or to increased hematocrit were censored from the study. Informed consent to participate in the study was required.

Epoetin Treatment

The objective of epoetin treatment was to gradually attain a stable increase of four points or more above baseline hematocrit. General recommendations for epoetin treatment were the following: When the baseline dose of epoetin was <60 U/kg per wk, the initial epoetin dose was doubled. If the baseline epoetin dose was >60 U/kg per wk, it was first increased by 50%, then doubled in 1 mo. The route of administration previously used was maintained. If the desired increase in hematocrit was not reached with these doses, the decision for subsequent dosage increases was left to the attending physician. Iron replacement was maintained by iron administration (preferentially intravenously), with monthly serum ferritin measurements. Our aim was to maintain the same serum ferritin level as before increasing the epoetin dose.

Evaluation of Health-Related Quality of Life and Functional Status

Two questionnaires were used to evaluate health-related quality of life: the Karnofsky scale (KS) and Sickness Impact Profile (SIP). Physicians instructed patients in the use of the forms, and all patients completed them at home on a non-dialysis day. None of them required any help from staff to complete them. In earlier controlled studies of patients on dialysis treated with erythropoietin in which the same health-related indicators were used (KS and SIP), erythropoietin treatment did not have a placebo effect, and bias did not enter the questionnaire responses, despite repeated completion of the questionnaires throughout the study period (1,4,5).

The KS is a global indicator of self-sufficiency and functional capacity (17). It consists of a 10-level scale, with scores ranging from 100 (normal, no limitations) to 10 (moribund). Higher scores indicate better functional status. Although the KS was originally designed to be evaluated by the physician, its reliability and validity when completed by the patients themselves have been repeatedly confirmed (18,19).

The SIP is a behavior-based questionnaire (20) that evaluates disease-related dysfunctional behavior. It is a non-pathology-specific quality-of-life indicator that has been used frequently in patients with chronic renal failure. It consists of 136 items grouped into 12 areas of activity (called partial SIP categories) in which dysfunctional behavior can occur. Individual items and partial categories are assigned values according to their relative importance. Three of the 12 categories (body care and movement, mobility, and ambulation) are grouped in a Physical Dimension, four (emotional behavior, social interaction, alertness, and communication) in a Psychosocial Dimension, and five (eating, work, home management, sleep and rest, and recreation and pastimes) are independent categories. The grouping of all partial categories produces the Global Dimension. Scores vary from 0 points (absence of dysfunction) to 100 points (maximum dysfunction). Lower scores indicate that the disease has less effect on quality of life. The Spanish version of the SIP, adapted for Spain from W. Hendricson's Hispanic version (21) by Dr. F. Moreno, was used in this study.

Other Determinations

Comorbidity was evaluated using the Friedman Comorbidity Index (22). To calculate this index, 13 pathology groups are evaluated on a 4-point scale (0, absent; 1, slight; 2, moderate; 3, severe), and the scores for all groups are added. Severity is estimated by the physician.

Other information collected includes social and professional situation, economic status (3-level scale: low, middle, and high), and educational level (5-point scale: 1, illiterate; 2, barely literate; 3, elementary school; 4, high school; 5, university). Blood chemistries were measured before dialysis. Hemoglobin, hematocrit, and serum ferritin levels were measured every month. Hemoglobin was measured by automated counter, serum ferritin was determined by enzyme immune assay, and serum albumin by bromcresol green. Serum albumin, Kt/V, and PCR were measured every 3 mo. The type of dialyzer and hemodialysis technique were noted (bicarbonate, acetate hemodialysis, hemodiafiltration). Kt/V and PCR were calculated according to Daugirdas-2 (23).

Statistical Analyses

Baseline and final scores on the quality of life and functional status indicators were compared using the Wilcoxon signed rank test (24). Survival tables (25) were used to evaluate the risk of vascular access thrombosis. Quantitative data are expressed in the text and tables as arithmetic mean ± SD. Prevalence of arterial hypertension was compared using the χ^2 test. Hospitalization rates were compared using the paired *t* test. Factors possibly related to changes in quality of life were studied using stepwise linear regression. All patients who began the study were included in the safety analysis.

Results

Patients

A total of 156 patients were included in the study. Seven patients left the study because they received a cadaver renal transplant, and 12 patients were censored due to adverse effects of the treatment. Twelve patients failed to show at least a 4-point increase in hematocrit figures during the follow-up period. Ten patients were lost due to a change in dialysis center. One hundred fifteen patients completed the 6-mo follow-up period.

The mean age of patients was 44 ± 15 yr and 61% were male. Mean time on dialysis was 36 mo (range, 3 to 216 mo). Nineteen percent had previously received a renal transplant. Table 1 shows the characteristics of the patients in the study. It should be noted that 8% of the patients were treated with hemodiafiltration, and that 82% of the patients who were hemodialyzed received bicarbonate. Forty percent of the patients were treated with a synthetic membrane dialyzer. With regard to the vascular access, it is important to note that only 30% of patients had a polytetrafluoroethylene (PTFE) graft; the other 70% had a native arteriovenous fistula.

Hemoglobin, Hematocrit, and Ferritin Levels

Mean baseline hemoglobin and hematocrit levels were 10.2 ± 0.7 g/dl and 31 ± 2%, respectively. Mean figures after 6 mo of follow-up were: hemoglobin 12.5 ± 0.9 g/dl and hematocrit 38.5 ± 2.5% (range, 36 to 43; median 38%). The mean increment in hemoglobin and hematocrit was 2.3 ± 0.9 g/dl and 7.5 ± 2.5%, respectively. Serum ferritin showed no significant change during follow-up (initial, 209 ± 164 ng/ml; final, 202 ± 132 ng/ml). Figure 1 shows the monthly evolution of hemoglobin and hematocrit figures.

One hundred of the 115 patients who completed the follow-up received iron treatment. The percentage of patients who received parenteral iron supplements increased from 61% at onset to 78% at the end of follow-up. The mean intravenous iron dose increased by 54% (baseline, 71 mg/wk; final, 109 mg/wk). The parenteral iron preparation used was always ferrous gluconate (Ferrlecit®).

Quality-of-Life Indicators

When comparing baseline and final scores for the quality-of-life indicators of the 115 patients who completed the study, we observed a significant reduction in the Physical Dimension, Psychosocial Dimension, and Global scores on the SIP (lower means better functional status) and an increase in scores on the KS (higher means better functional status) (Table 2 and Figure

Table 1. Patient characteristics[a]

Characteristic	Mean (SD)
Quantitative data	
age (years)	44 (15)
months on dialysis	37 (40)
Friedman Comorbidity Index	3 (2)
Kt/V	1.17 (0.3)
PCR	1.2 (0.3)
Hb (g/dl)	10.2 (0.7)
Hct (%)	31 (2)
Qualitative data	
gender	Male 60%/Female 40%
previous failed renal transplant	19%
hemodialysis technique	HD 92%/HDF 8%
hemodialysis buffer	Bicarbonate 82%/Acetate 18%
dialyzer membrane	Cellulosic 60%/Synthetic 40%
vascular access	PTFE graft 30%/Native fistula 70%

[a] Hb, hemoglobin; Hct, hematocrit; HD, hemodialysis; HDF, hemodiafiltration; PTFE, polytetrafluoroethylene.

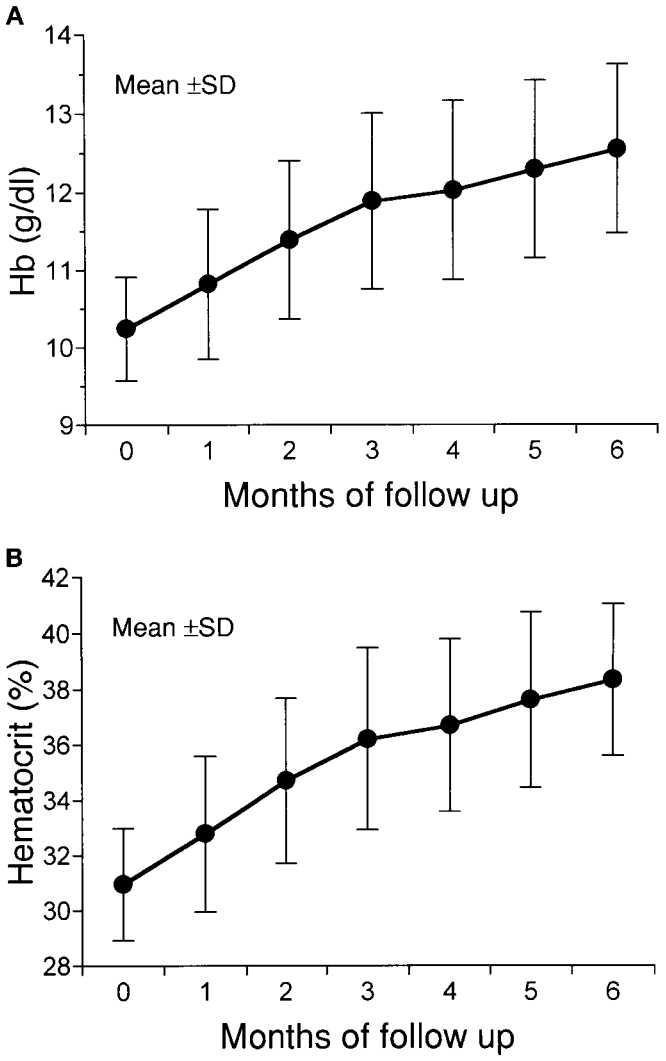

Figure 1. Changes in hemoglobin level (A) and hematocrit (B) during the study (mean ± SD).

2). These changes indicate a significant improvement in the quality of life and functional status of patients.

Nutritional Parameters and Dialysis Efficiency

No significant changes were observed during the study in mean PCR values (from 1.2 ± 0.3 to 1.2 ± 0.3), serum albumin (from 4.3 ± 0.4 to 4.2 ± 0.5 g/dl), and Kt/V (from 1.17 ± 0.2 to 1.17 ± 0.2). The same dialyzer and dialysis techniques were used for all patients throughout the study.

Epoetin Treatment

Epoetin was administered subcutaneously to 53% of patients and intravenously to 47%. All patients continued with the same administration route throughout the follow-up period. The mean initial epoetin dose was 93 ± 62 U/kg per wk and the final dose was 141 ± 80 U/kg per wk, a 51% increase in mean epoetin consumption.

Table 2. Changes of quality-of-life indicators between onset (mean hemoglobin 10.2 g/dl) and after 6 mo (mean hemoglobin 12.5 g/dl)[a]

Indicator	Mean (SD)	Median	*P* Value[b]
SIP Physical Dimension			
baseline	5.4 (1.2)	3.3	<0.005
final	4.1 (1.12)	1.2	
SIP Psychosocial Dimension			
baseline	9.2 (1.8)	6.8	<0.001
final	7 (1.7)	4.6	
SIP Global score			
baseline	8.9 (1.39)	7.9	<0.001
final	7.25 (1.3)	5.5	
Karnofsky scale			
baseline	75.6 (2.7)	80	<0.01
final	78.4 (2.8)	80	

[a] Lower scores mean better quality of life on the SIP. Higher scores mean better quality of life on the Karnofsky scale. SIP, Sickness Impact Profile.
[b] Wilcoxon signed rank test.

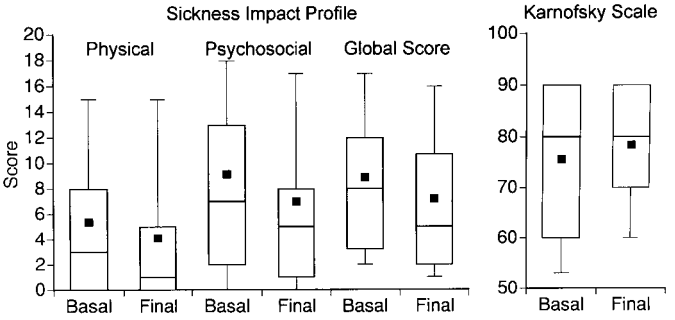

Figure 2. Box plot of quality-of-life indicators. The top and bottom lines and the line through the middle of the boxes correspond to the 75th percentile, 25th percentile, and 50th percentile (median), respectively. Error bars correspond to the 90th percentile (top) and 10th percentile (bottom).

Adverse Effects

No patient died in the 6 mo of follow-up. Nine patients (5.7%) were censored from the study because of vascular access thrombosis. The cumulative probability of developing thrombosis over the 6-mo study period was 0.067.

Three patients (2%) were censored for hypertension that was difficult to control. One of them had a hypertensive emergency with cardiac failure. There were no significant changes in the prevalence of arterial hypertension (Table 3) or in mean BP during follow-up in the 115 patients who completed the study. No other adverse effects attributable to epoetin treatment or to increased hematocrit were detected.

Epoetin dose was lowered to the baseline level in all patients censored during the study for thrombosis of the vascular access or severe hypertension, and they were followed up throughout the 6-mo study period. None of them had further complications.

Table 3. Prevalence of arterial hypertension

Category	Baseline	3 Months	6 Months	χ^2
Hypertensive	68	62	66	P = NS
Normotensive	47	53	49	

Hospitalization

To evaluate the possible influence of increased hematocrit on hospitalization, the number of admissions and length of hospital stay in the 6 mo preceding the study were compared with those occurring in the study period. Table 4 shows the results of this comparison. A 58% reduction in number of hospitalizations and a 69% reduction in duration of hospital stays were observed ($P < 0.05$).

Variables Related to Quality-of-Life Indicators

The following factors were studied in relation to their possible influence on the evolution of quality-of-life indicators: age, gender, time on hemodialysis, comorbidity index, previous failed renal transplant, socioeconomic and educational status, hemodialysis technique, epoetin dose, increase in hemoglobin and hematocrit levels, initial and final hemoglobin and hematocrit, albumin, Kt/V, and PCR. Forward stepwise linear regression models were constructed using the change in scores on the quality-of-life indicators as the dependent variables. The above-described factors and initial scores of the quality-of-life indicators were used as independent variables. Goodness of fit was assessed with residual analysis. The robustness of regression results obtained with all patients was checked by constructing models without outliers (standardized residual >3) after excluding outliers and the 10 patients with the most extreme figures for dependent variables (the five who deteriorated most and the five who improved most). Table 5 shows some results of the regression studies. Only the baseline score of each quality-of-life indicator was consistently related to improvement. Lower quality of life was related to greater improvement in quality-of-life scores after increasing hemoglobin. Other variables initially related to improvement in the quality-of-life indicator scores lost their significance after deleting outliers and cases with extreme dependent-variable values.

Table 4. Influence of increased hemoglobin levels on hospitalization[a]

Variable	6 Previous Months		6 Months of Study		*P* Value[d]
	Total[b]	Mean[c]	Total	Mean	
No. of hospitalizations	19	0.17	8	0.07	<0.05
Length of hospital stay (days)	152	1.3	47	0.4	<0.05

[a] The total number of hospitalizations and length of hospital stay during the study period were compared with those occurring in the 6 mo preceding the study in the same patients.
[b] 115 patients.
[c] Mean by patient.
[d] Paired *t* test.

Discussion

Target hematocrit/hemoglobin values for the treatment of anemia in dialysis and predialysis patients remains a matter of controversy. Published studies show that normal hematocrit/hemoglobin levels benefit these patients. The beneficial effect of normalizing hematocrit has been confirmed by the improvement observed in cognitive function, physical function, quality of life, and cardiovascular mortality. The maximum level of oxygen delivery to the brain occurs within a hematocrit range of 40 to 45% (26), and the brain function of dialysis patients improves with normal hematocrit. In a study of event-related potentials and neuropsychological function by psychometric tests, a significant improvement was found when the mean hematocrit of dialysis patients increased from 23.7 to 36.4% with epoetin treatment (14,15). A close relationship between end-stage renal disease-related anemia and sleep has been shown. The beneficial effects on sleep of normalizing hematocrit (from 32.3 to 42.3%) was demonstrated by studying several indexes (16).

The beneficial effect of a normal hematocrit on physical function has been extensively shown. In predialysis patients, energy and work capacity improved more when anemia was completely corrected (10). VO_2 is higher at a hematocrit of 35 to 40% than at 30% (11). In another study of hemodialysis patients, increasing mean hematocrit from 32.6 to 42% had the following effects: maximal oxygen uptake increased by 24%, bicycle exercise increased by 20%, pulmonary CO diffusion increased by 54 to 64%, and quadriceps isometrics increased (12). Finally, a more recent study shows a significant increase of maximal exercise performance (peak work rate and peak VO_2) in hemodialysis patients whose hemoglobin level increased from 10 to 14 g/dl (13).

Quality of life in dialysis patients is better at higher hematocrit levels (5–7), and the present study confirms that the normalization of hematocrit/hemoglobin significantly improves the Physical and Psychosocial Dimensions of quality of life and the patient's functional self-sufficiency. The study by Besarab *et al.* (9) showed that an increase in hematocrit from 30 to 42% was associated with a clinically meaningful increase of 7.2 points in the score of the physical function scale.

The strict criteria used to select the patients included in our study (nondiabetic patients, without severe cardiovascular and cerebrovascular comorbidities or severe associated disease, and age under 65 yr) do not reduce the external validity of the results obtained, but limit their applicability to a select group of patients. According to earlier findings by our group (5), almost 50% of dialysis patients in Spain meet the selection criteria used in the present study.

An important finding of this study was the low rate of adverse cardiovascular effects. The onset or aggravation of arterial hypertension is one of the main complications related to epoetin treatment. In our study, only one patient had a sudden, hypertensive emergency with cardiac failure. The slow

Table 5. Factors related to improvement in quality-of-life indicators

Dependent Variable	Forward Stepwise Linear Regression: Selected Independent Variables	Corrected r^{2a}	Standardized β Coefficients (last steep)
Improvement in Global score of SIP			
all cases	1—Basal Global score[b]	Steep 1: 0.14	0.4
excluding outliers	1—Basal Global score[b]	Steep 1: 0.18	0.5
	2—Educational level[c]	Steep 2: 0.21	0.2
Improvement in Physical Dimension score			
all cases	1—Basal Physical Dimension[b]	Steep 1: 0.20	0.5
	2—Gender[d]	Steep 2: 0.23	−0.2
excluding outliers	1—Basal Physical Dimension[b]	Steep 1: 0.27	0.6
	2—Economic status[e]	Steep 2: 0.30	0.2
	3—Final albumin	Steep 3: 0.33	0.2

[a] Corrected determination coefficients for regression steeps.
[b] Higher scores indicate worse functional status.
[c] 1, illiterate; 2, barely literate; 3, elementary school; 4, high school; 5, university.
[d] 0, male; 1, female.
[e] 1, low; 2, middle; 3, high.

increase in hematocrit/hemoglobin levels, reaching desired hematocrit at 2 to 3 mo, probably played an important role in the low incidence of adverse cardiovascular effects.

In the study by Besarab *et al.* (9), which included 1233 hemodialysis patients with heart disease, the group in which hematocrit was raised to normal levels (42 ± 3%) had higher mortality than the control group, in which hematocrit was kept at 30 ± 3%. This caused the study to be suspended. Based on these results, the authors advised against raising hematocrit to normal levels in hemodialysis patients with heart disease. However, this study only included high cardiac risk patients (patients with ischemic heart disease or congestive heart failure), and the increased mortality was unrelated to hematocrit and due to cardiovascular causes. This study has been analyzed and criticized in interesting editorials (27,28).

Anemia has been shown to be a risk factor for mortality, morbidity, and hospitalization (29–32). Ma *et al.* (31) studied the association between hematocrit levels and patient mortality in a prevalent Medicare hemodialysis cohort on a national scale. Their results showed that patients with hematocrit levels of <30% had a significantly higher risk of death compared to patients with a hematocrit in the 30% to <33% range. Patients with hematocrit levels in the range of 33 to 36% appear to have the lowest risk of death.

A significant decrease in the number of hospitalizations and length of hospital stay was observed in our patients, compared to the 6 mo previous to the study in the same patients. However, this should be interpreted carefully because the follow-up period of our study lasted only 6 mo. These findings coincide with those reported by Xia *et al.* (30,31). In a total of 71,717 dialysis patients, they found a lesser probability of hospitalization with hematocrit levels of 33 to 36% than in patients with lower hematocrit levels.

The incidence of thrombosis of the vascular access in hemodialysis patients varies widely in different studies. The Canadian Hemodialysis Morbidity Study (33) reports an annual incidence of 24.5% in non-epoetin-treated patients, and the Canadian Erythropoietin Study Group (34) shows a 78-wk incidence of 17% in epoetin-treated patients. Other authors have found lower rates of vascular access thrombosis in patients treated with epoetin, ranging from 0.09/patient-year in patients with native fistulae to 0.9/patient-year in patients with PTFE grafts; the overall rate was 0.5/patient-year (35,36). In our study, the cumulative probability of vascular access thrombosis was 0.067 at 6 mo. It is important to remember that only 30% of our patients had PTFE grafts.

Another aspect analyzed in the present study was the effect of normalizing hematocrit on heath care costs. We found a 51% increase in mean epoetin consumption by the end of the study. A cost-benefit analysis of our findings must take into account both the higher cost of increased iron and epoetin doses, and the significant reduction in the number and length of hospital stays. Almost half of the patients (47%) received epoetin intravenously. Changing the administration route from intravenous to subcutaneous would probably have reduced costs, according to recent findings (37). The epoetin doses used on our patients, both at baseline and during the study period, were lower than those reflected in other studies (9). This may be partially due to the fact that the patients selected did not have any acute or chronic intercurrent processes that could negatively affect the response to epoetin. The extensive use of intravenous iron supplements could also have contributed to higher treatment efficiency.

In summary, our findings suggest that a blanket policy against normalization of hematocrit levels is not justified and that normalization of hematocrit levels in selected hemodialysis patients improves quality of life and functional status without severe adverse effects. The target hematocrit for the treatment of anemia in patients with end-stage renal disease should be reconsidered and systematically related to risk factor-based

groupings of patients. In adult nondiabetic patients under 65 yr old who have no significant comorbidity, our results suggest that the target hemoglobin/hematocrit should be as close to normal as possible. In patients with diabetes, severe comorbidity, and advanced age, extensive studies are required to confirm the safety and beneficial effects of increasing hematocrit to normal levels with epoetin.

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Appendix

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