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Original Article

Effect of Increased Hemodialysis Time on the Response to Erythropoietin in Patients with End-Stage Renal Disease

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ABSTRACT

Background: A cost-effective use of epoetin requires that the maximum gain in hematocrit level be obtained for a given dose. If such could be achieved, it would justify the use of scarce health care resources for epoetin treatment.

Objectives: The aim of the work was to determine the effect of increase in the time of dialysis on the hematocrit in epoetin-treated hemodialysis patients.

Methods: We prospectively studied 60 anemic patients undergoing bicarbonate hemodialysis with hemophan membranes for a follow-up duration of 12 weeks. Patients were randomized into 4 equal groups. Groups A & C were dialyzed for 4 hrs thrice weekly and groups B & D for 6 hrs thrice weekly. Group C & D patients received a fixed dose of epoetin. We investigated the relationship between dialysis time, URR, and the percent change in hematocrit.

Results: With increase in dialysis time there was a highly statistically significant difference in mean URR in group B from 0.594 ± 0.03 to 0.722 ± 0.03 at the beginning and after 12 weeks respectively with a % change of 20.5 ($p < 0.01$) and group D from 0.596 ± 0.02 to 0.749 ± 0.03 with a % change 25.85 ($p < 0.01$). There was a highly significant difference between groups in mean hematocrit at the beginning of the study (group D had the lowest value). The highest hematocrits were achieved in group B from a mean of 24.74 ± 5.07 to 31.09 ± 3.56 at the beginning and after 12 weeks respectively with a % change of 28.9 ($p < 0.01$) and in group D from 19.31 ± 3.23 to 32.13 ± 3.49 with a % change of 69.8 ($p < 0.01$) while group A had the lowest level from 24.67 ± 3.78 to 25.46 ± 3.68 with a % change 4.2. There was a significant positive correlation between URR and the change in hematocrit (coefficient of correlation 0.44).

Conclusions: We conclude that dialysis time appears to be an important independent factor predicting response to epoetin. In a country with limited resources, where treatment expenses are first priority, we recommend that using epoetin, with its consequent impact on the cost of management, must be coupled with optimizing the dose of dialysis by increasing dialysis time.

INTRODUCTION

The state of uremia inhibits erythropoiesis. Several factors have been suggested as being involved in this process, including the polyamines, parathyroid hormone, and various cytokines. The suppression of erythropoiesis, however, can be easily overcome by exogenous erythropoietin administration[1]. Effective treatment of renal anemia with epoetin improves survival[2] and increases quality of life[3]. There is also evidence that underdialysis may cause a degree of hyporesponsiveness to erythropoietin therapy, resulting in higher dosage requirements[4].

ESRD patients on dialysis manifest anemia modulated by dialysis dose. An increase in the dialysis dose raises the hematocrit with a concomitant decrease in the endogenous erythropoietin level, suggesting enhanced removal of inhibitors of erythropoiesis[5].

Many factors influencing response to epoetin can be controlled: iron and epoetin supplementation policies, water quality and factors that influence dialysis adequacy, such as the choice of dialysis filter, dialysate and blood flow rates, and duration of dialysis.

The National Cooperative Dialysis Study, showed a clear relationship between dialysis duration and hematocrit[6]. Another study with patients treated with long-duration dialysis, but without epoetin, reported hematocrits as high as 28%[7].

Movilli et al.[8], investigated the relationship between epoetin and dialysis dose in patients on conventional hemodialysis, and concluded that Kt/V was the only significant variable independently contributing to epoetin dose, suggesting that dialysis adequacy per se can influence anemia.

The dialysis time per se, independently from dialysis adequacy, may have a role in the correction of anemia, but this probably has never been tested properly[9].

AIM OF THE WORK

The aim of the work was to determine the effect of increase in the time of dialysis on the hematocrit in epoetin-treated hemodialysis patients.

SUBJECTS AND METHODS

The study included sixty patients with normocytic normochromic anemia and a hematocrit of less than 30% from a pool of 80 patients with ESRD sustained by maintenance hemodialysis thrice weekly for at least 3 months, age 20 years and older, not receiving drugs known to affect erythropoiesis (androgens, steroids), at the outpatient hemodialysis facility in Al Hussein University Hospital.

Patients were excluded if their transferrin saturation was < 25% or serum ferritin was < 200 ng/ml or an MCV of < 85 fl (to exclude iron depletion) or > 100 fl (to exclude B12 or folate depletion). Patients were also excluded if their PTH was > 500 mU/ml, or were using aluminum hydroxide-based binders.

Patients satisfying the criteria were randomized into 4 groups:

Group A: 15 patients not receiving Epo on a 4 hrs thrice weekly schedule.

Group B: 15 patients not receiving Epo on a 6 hrs thrice weekly schedule.

Group C: 15 patients, receiving Epo on a 4 hrs thrice weekly schedule.

Group D: 15 patients, receiving Epo on a 6 hrs thrice weekly schedule.

Group C & D patients were treated with a fixed dose of Epo 2000 IU (s.c) at the end of dialysis session, for the follow-up period of 12 weeks, and all patients received regular I.V iron supplements.

To assess the intensity of dialysis, we calculated the percent reduction in BUN (predialysis BUN – post dialysis BUN / predialysis BUN x 100).

Every 4 weeks throughout the 12 week study period, BUN, serum creatinine, cholesterol, triglycerides, albumin conc. red cell count, MCV, MCH, MCHC, hemoglobin and hematocrit were recorded.

Statistical analysis

Data were analysed using Epi-info software version 6.04, 2001 (WHO).

Means, Anova or F test were done to measure significant differences between means of more than two groups.

Chi-square was done to test significant relations between percentages.

Percentage change = value of 1st testing – value of 2nd testing / value of 1st testing x 100.

Significant results were considered if $p < 0.05$.

RESULTS

All groups were comparable regarding age, gender distribution, duration of dialysis, and body weight at the beginning of the study [Table 1].

There was no significant difference between groups at the beginning of the study in mean value of serum albumin. After 12 weeks there was a highly significant difference between groups ($F = 5.73$, $p < 0.001$) in mean value of albumin. The increase in mean serum albumin in group B was from 3.46 ± 0.31 to 3.74 ± 0.28 with a significant percent change of 7.7 ($p < 0.05$) and highest in group D from 3.76 ± 0.38 to 4.04 ± 0.43 with a significant percent change of 9.22 ($p < 0.05$).

Table (2) shows a highly statistically significant difference between groups in URR after 12 weeks. The percentage change was significantly different between groups. Groups B & D had the highest % change in URR.

There was a highly significant difference between groups in hematocrit value at the beginning of the study (group D had the lowest level), after 4 weeks (group D & A had the lowest level), and after 12 weeks (group A had the lowest level). The percent change in hematocrit value was highest in groups C & D [Table 3].

The percent change in hemoglobin was highest among groups C & D [Table 4].

There was a significant positive correlation between URR and the time of dialysis session (coefficient of correlation 0.82) and the change in hematocrit (coefficient of correlation 0.44).

Table 1: Comparison between studied groups in age, gender, time of dialysis and body weight.

Variables		Group A	Group B	Group C	Group D	p
Age	Range	26-58	23-60	21-58	21-63	F = 2.35
	Mean ± SD	49.67 ± 8.47	43.93 ± 10.47	42.07 ± 11.06	39.73 ± 12.45	p > 0.05
Gender	Male	8 (53.3%)	7 (46.7%)	7 (46.7%)	8 (53.3%)	X = 0.42
	Female	7 (46.7%)	8 (53.3%)	8 (53.3%)	7 (46.7%)	p > 0.05
Duration of dialysis (months)	Range	11-80	12-84	11-85	9-81	F = 2.62
	Mean ± SD	42.2 ± 22.48	49.64 ± 26.19	47.43 ± 26.45	40.2 ± 23.51	p > 0.05
Weight	Range	50-96	50-95	35-81	35-86	F = 2.62

Table 2: Percentage change in URR on follow-up for cases of the studied groups.

Group	URR		% change
	At the beginning	After 12 weeks	
A	0.593 ± 0.03	0.595 ± 0.02	1.6
B	0.594 ± 0.03	0.722 ± 0.03	20.5**
C	0.597 ± 0.03	0.611 ± 0.02	4.3*
D	0.596 ± 0.02	0.749 ± 0.03	25.85**
F	0.09	118.57	37.95
p	> 0.05	< 0.0000	< 0.000

* $p < 0.05$ = significant % change.
** $p < 0.01$ = highly significant % change.

Table 3: Percentage change in hematocrit level among groups on follow-up.

Group	HCT						
	At the beginning	4 weeks	% change after 4 weeks	8 weeks	% change after 8 weeks	12 weeks	% change after 12 weeks
A	24.67 ± 3.78	23.63 ± 3.57	-3.55	25.02 ± 4.37	2.50	25.46 ± 3.68	4.2
B	24.74 ± 5.07	27.77 ± 3.61	12.35	29.14 ± 3.74	20.46	31.09 ± 3.56	28.9**
C	22.19 ± 5.25	25 ± 6.07	16.93	27.77 ± 5.12	28.57	29.55 ± 5.01	37.4**
D	19.31 ± 3.23	22.52 ± 3.45	16.04	26.31 ± 3.95	37.13	32.13 ± 3.49	69.8**
F	5.07	3.34	6.58	2.46	7.95	8.12	16.79
p	< 0.01	< 0.05	< 0.001	> 0.05	< 0.001	< 0.001	< 0.0001

* $p < 0.05$ = significant % change
** $p < 0.01$ = highly significant % change

Table 4: Percentage change in hemoglobin on follow-up of cases at the different studied groups.

Group	At the beginning	4 weeks	% change after 4 weeks	8 weeks	% change after 8 weeks	12 weeks	% change after 12 weeks
A	8.71 ± 1.37	8.37 ± 1.22	-3.44	8.65 ± 1.53	0.88	8.92 ± 1.15	4.60
B	8.72 ± 1.46	9.41 ± 1.13	9.05	10.04 ± 1.02	16.56	10.62 ± 1.26	23.3**
C	7.29 ± 1.71	8.42 ± 1.94	21.04	9.37 ± 1.76	31.84	10.05 ± 1.79	41.7**
D	6.73 ± 1.04	7.8 ± 1.16	16.27	9.11 ± 1.41	36.38	11.05 ± 1.18	65.8**
F	7.54	3.38	8.35	2.29	10.52	6.82	18.32
P	< 0.001	< 0.05	< 0.001	> 0.05	< 0.001	< 0.001	< 0.001

* $p < 0.05$ = significant % change.
** $p < 0.01$ = highly significant % change.

DISCUSSION

There are many risk factors determining the clinical outcome in hemodialysis patients. Among them, the dose of dialysis and malnutrition are considered to play the major role, and they have been shown to be highly associated with increased morbidity and mortality in ESRD patients[10].

In our study, all groups were comparable regarding age, gender distribution, body weight, and duration of dialysis.

Increasing the dose of dialysis by increasing the time of the session from 4 hrs to 6 hrs was associated with the highest percent change in URR and was associated with a significant increase in albumin, cholesterol, and triglycerides. However, the relationship between dose of dialysis and nutritional status is still unclear. It was demonstrated that patients given higher than conventional dialysis dose, experienced improved serum albumin level. It is reasonable to assume that higher URR could remove excessive uremic toxins and thereby improve appetite[11].

In our study, in spite of a significant increase in hemoglobin and hematocrit in the group of patients with increased dialysis dose without receiving Epo, the percent change in hematocrit was highest among the group with increased dialysis dose and receiving Epo.

Ifudu and Friedman, in 1998, stated that the improvement in anemia following delivery of good dialysis is not due to increased endogenous erythropoietin production. Also, in the prerecombinant erythropoietin era, patients who were dialyzed thrice weekly had higher hematocrit[12].

The correlative analysis in our study

showed a significant positive correlation between the URR, the duration of dialysis, and the hematocrit change.

We did not question the potential of erythropoietin to expand red-cell mass in patients with ESRD but the correction of anemia resulting from an increased level of dialysis. In addition Movilli et al., in 2001, concluded that by optimizing Epo responsiveness, an adequate dialysis treatment can contribute to a reduction of the costs of Epo therapy.

In conclusion, our results stress the importance of adequate dialysis, not as a tool for reducing the morbidity and mortality of hemodialysis, but also for optimizing epoietin responsiveness and achieving anemia correction.

In a country with limited resources, where treatment expenses are first priority, we do recommend using Epo, with its consequent impact on the cost of management, coupled with increasing the dose of dialysis by increasing dialysis time.

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