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Research Article

Inter- and Intra-Patient Cyclical Variability in Hgb Responses in Patients on Hemodialysis and Online Hemodiafiltraion

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Abstract

Objective: To study the variability in Hgb response to standard anemia management guidelines in hemodialysis patients.

Methods: This is an observational prospective study on stable chronic dialysis patients. Baseline Hgb and iron studies were performed during the monthly anemia management rounds and repeated after a one-month cycle. ESA and IV iron dose adjustments were made according to a standard protocol.

The variability in Hgb change and its relation to gender, type of ESA, dialysis modality, vascular access type, ESA and IV iron therapy adjustment and baseline hematological parameters were analyzed.

Results: Of 222 patients included, 77.3% were on hemodialysis (HD) and 22.7% on hemodiafiltation (HDF).

Darbepoetin was in 31.9% and EPO in 68.1% of the patients.

Over the observation period, the ESA dose was unchanged in 40.8%, withheld in 8.3%, reduced in 18.8% and increased in 26.6 % while the Hgb level rose in 56.4%, dropped in 8.5 % and was unchanged in 35.5% of the patients. However, the overall frequency of patients with hemoglobin levels in the recommended range did no change (64.7% and 63.2% respectively (p= 0.83).

Neither the magnitude nor the direction of ESA dose adjustment nor the change in Hgb level or its direction were affected by the ESA type, the dialysis type , the vascular access type or IV iron therapy given .

No differences were noted between the HD and HDF groups in any of the parameters measured except that HD group required higher darbepoetin dose (56.6 ± 43 mcg versus 35.5 ± 30 mcg) in HDF group (p=0.031).

No differences were noted between the patients using permcaths as vascular access and those with native grafts in any of the parameters measured except that the former group required higher darbepoetin dose (13915 ± 9635 iu and 10150 ± 8877 iu respectively p=0.02).

Conclusion: Although there was no change in the proportion of patients with Hgb levels within the recommend range over the observation, period, the change in Hgb level was not always predictable by the ESA dose adjustment magnitude or direction. There was a significant increase in the number of patients h Hgb levels between >13 gms from 5.4% to 10.5% (p=0.0001).

Patient on HD required higher darbepoetin dose than those on HDF despite similar hematological parameters findings and IV iron usage in both groups.

Patient using Permcaths for vascular access required higher darbepoetin dose than those with native grafts despite similar hematological parameters findings and IV iron usage in both group.

Keywords: ESA; Hemodialysis; Hgb; HD; HDF

Introduction

The use of ESAs has revolutionized anemia management in dialysis patients. The usual protocols of anemia management that requires frequent Hgb measurement and therapy adjustment often lead to considerable hemoglobin cycling with greater than 90% of patients experiencing this cycling [1]. Hemoglobin cycling, which has been shown to be often facility and even country related [2] can be harmful and associated with increased mortality [2-4] and is time

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Table 1: Baseline characteristics.

% Males	41.1 %
% Female	58.9%
% on HD	77.3%
% on HDF	22.7%
% patients using darbepoetin	31.9%
% patients using EPO	68.1%
Mean Serum iron	9.4±4.5
Mean TIBC	33.4±7.1
Mean TSAT	31.0±12.0
	Mean± STD
Age (years)	57.8±19.2
Aranesp Weekly dose (mcg)	50.8±40.8
Epo Weekly dose (iu)	11748.2±9360.8

Table 2: ESA dose according to the vascular access or dialysis type uses.

	Vascular access type	Mean	p
Darbepoetin Wkly	AVF/AVG	54.4 ±45.7	0.45
	Permcath	46.8±35.1	
Epo /week	AVF/AVG	10150± 8877	0.02
	Permcath	13915±9635	
	Mode of RX	Mean	
Darbepoetin Wkly	HD	56.6±43	0.031
	HDF	35.5±30	
Epo /week	HD	12146±9338	0.35
	HDF	10300±9458	

consuming and labor-intensive for the unit staff.

It has been claimed that the variability in response to ESA can be assessed using erythropoietin resistance index (ERI), (calculated as the weekly weight-adjusted dose of EPO divided by the hemoglobin level). The ERI was found to be directly related to existing comorbidity age, female gender and low body mass index and inversely related to the transferrin saturation index but not to serum ferritin. Higher ERI was observed in patients using permcaths as vascular access than in patients with native fistula [5].

In this study, we aim to investigate the variability in the changes in Hgb levels under standard ESA dose and iron dose adjustment guidelines and factors that effect this variability.

Methods

This observational prospective study evaluated anemia management practice in our center. All the patients on hemodialysis for 6 months or more were included in the study. Patient with acute illness, malignancy or active inflammatory diseases were excluded. Baseline Hgb, ferritin, total iron binding capacity (TIBC), serum iron, and transferrin saturation (TSAT) were measured during one routine monthly anemia management round. Decisions based on unit guidelines regarding ESA dose adjustment (hold, keep unchanged, increase or decrease) and IV iron regimen (none, maintenance or loading doses given) were recorded. These decisions were based on the need to achieve hemoglobin levels in the ranges recommended by NKF-DOKI guidelines [6]. The hemoglobin and ferritin levels one month later were measured and change calculated.

The variability in Hgb change and its relation to gender type of ESA used, gender, dialysis modality and vascular access type was investigated.

Descriptive statistics were generated using SPSS version 21. Calculation of significant differences were carried out using Chi square for proportions and non-parametric data and paired sample test and one way ANOVA for parametric data.

Results

The number of patients included in the study was 222 with a mean age of 57.8 ± 19.2 years. All were on three times weekly dialysis for at least 6 months prior to inclusion in the study; 58.9% were female, 77.3% were on HD and 22.7% on HDF and with a mean Kt/V of 1.5 ± 0.2. Darbepoetin was the ESA used in 31.9% of the patients (mean dose of 50.8 ± 40.8 mcg/week) and EPO in 68.1% of the patients (mean dose of 11748.2 ± 9360.8 iu/week) (Table 1). The mean serum iron, TIBC and TSAT at baseline were 9.4 ± 4.5, 33.4 ±7.1and 31 ± 12.0 respectively.

In 12.8% of the patients no IV iron was prescribed, in 76.6%, a maintenance iron regimen was given and in 10.6 %, a loading iron regimen was prescribed. These percentages were similar in the HD and HDF groups.

At baseline, only 60.9% and 64.7%of the patients had ferritin and hemoglobin levels in the recommended ranges (>200 & <600) and (110-130) respectively. These percentages did not change significantly one month after baseline (66.3% and 63.2% respectively). However, there was a significant increase in the number of patients with Hgb levels >13 gms from 5.4% to 10.5% (p=0.0001).

Of all the patients studied, 17.5% had a TSAT level of <20 and 32% had a level over 35% at baseline.

The mean change in Hgb level was not affected by type of ESA, type of dialysis (HD or HDF), gender or type of vascular access.

Similarly, the direction of the change in Hgb (unchanged, rose or dropped) was not affected by type of ESA (P= 0.25), mode of dialysis (HD vs. HDF) (P= 0.125) or vascular access type (P= 0.22).

Of all the patients studied, the ESA dose was unchanged in 40.8% , withheld in 8.3% , reduced in 18.8% (by 25%, 50% and 75% in 14.2%. 3.7% and 0.9% respectively) and increased in 26.6 % (by 25%, 50% and 75% in 18.3%. 3.7% and 4.6% % respectively).

Whereas, the weekly dose of darbepoetin was similar regardless of the vascular access used (p=0.45), the weekly dose of darbepoetin used in the patients with permcaths was significantly higher than that used in those with AVF/AVG (13915 ± 9635 and 10150 ± 8877 respectively p=0.02) (Table 2).

Although the weekly dose of EPO was higher in the HD group (12146 ± 9338 iu) compared to the HDF group (10300 ± 9458 iu), the difference did not reach statistical significance (p=0.35). On the other hand, the weekly dose of darbepoetin used in the patients on HD (56.6 ± 43 mcg) was significantly higher than that used in those

Table 3: Change in Hgb levels according to the magnitude and direction of ESA dose adjustment.

Direction of ESA dose adjustment	Mean change in Hgb ±std	P value
Hold	-2.72±16.0	Not significant comparing any type of adjustment to any other type of adjustment
Same dose	4.62±15.0	
Reduce 25%	3.58±11.1	
Increase 25%	2.95±14.9	
Reduce 50%	1.5±11.8	
Increase 50%	0.63±11.4	
Reduce 75%	2.5±20.5	
Increase 75%	4.8±15.1	

on HDF (35.5 ± 30 mcg) p=0.031) (Table 2). We found that the final Hgb level, compared to baseline HB level was higher in 56.4% of the patients, lower in 8.5 % and was unchanged in 35.5% of the patients. It is of note that the mean changes in hemoglobin levels were similar regardless of the dose or direction in ESA adjustment made (Table 3).

Discussion

Although various presumed evidence based guidelines have been recommended for anemia management in patients on dialysis, practitioners still find it difficult to attain the desired outcome [6,7]. Furthermore Hgb level cycling is a common occurrence [1].

When reviewing the routine monthly anemia management in these patients, the physician has to consider a number of complex management lines. These include possible ESA dose adjustment (and in what direction) and possible need for IV iron therapy (and if so at what loading and/or maintenance dose). Additionally, the physicians have to determine if they are dealing with an ESA non-responsive or resistant case and decide on the cause of this and its management [8]. It has been shown, for example, that fewer than 50% of patients had hemoglobin values within the NKF-K/DOQI recommended range [7].

In our study, we found that, at baseline, the frequency of Hgb level within recommended range in our center (110-130) to be only 60.9%. In the final observation, we found that this percentage remained the same although the actual patients with levels within the recommended range differed. In fact, we found that the final Hgb level, compared to baseline HB level was higher in 56.4% of the patients, lower in 8.5 % and was unchanged in 35.5% of the patients. Moreover, these directional changes in the hemoglobin level did not exactly mirror the directional changes in the ESA dose (18.8% of the patients had their ESA dose reduced, 26.6% had their dose increased and only 40.8% had their dose unchanged). Although the Hgb level rose in 56.4% of the patients, the percent of patients who were given IV iron loading because of low TSAT over the same period was only 10.6% suggesting that this Hgb rise was caused by causes, other than iron deficiency.

In the USA, the median Hgb of all the patients dropped from 12.1 g/dL prior to 2007 to 11.8 g/dL in 2010. Over the same period, the rate of patients on HD for more than 6 months who had hemoglobin level of >12 g/dL dropped from of 46% (prior to 2007) to 30% (in 2010). Concomitantly, the weekly Epoetin alpha dose dropped from 9100 units to 7800 units weekly. Iron doses, serum ferritin, and transferrin saturation levels increased over time with more pronounced increases in 2010 [9,10]. Whether HDF reduces ESA resistance is controversial. In one study, it was found that treatment with online HDF did not result in a decrease in ESA resistance [11]. Conversely, Lin et al., in their study, concluded that on-line HDF results in reduced EPO resistance and improved iron utilization [12].

In our study, on the other hand, we found that the type of dialysis (HD versus HDF) did not affect IV iron dosing given or the mean change in Hgb level or the direction of the change. Nevertheless, we found that the weekly dose of darbepoetin used in the patients on HD was 1.6 times higher than that used in those on HDF. Similarly, the type of ESA used (darbepoetin versus epoetin) did not affect the mean change in Hgb level or the direction of the change.

Whereas the weekly dose of darbepoetin was similar regardless of the vascular access used, the weekly dose of epoetin used in the patients with Permcath was significantly higher than that used in those with AVF/AVG (1.4 fold increase). This is consistent with other reports that indicate that permcaths use as vascular accesses are associated with need for higher doses of ESA secondly to blood loss during dialysis and possible catheter related infections [13]. In a study in children on dialysis, it was found that mean Hgb level was lower in patients with a central venous catheter as vascular access for dialysis compared to AVF [14]. As a result of the frequent occurrence of Hgb cycling, it has been suggested that this cycling and variability could be minimized by widening the target hemoglobin level range and by increasing the hemoglobin assessment interval form monthly to 3 to 6-montly intervals [7].

Berns et al., using epoetin as the ESA noted that that hemoglobin variability was reduced progressively with longer intervention intervals. The 25th to 75th percentile hemoglobin range was 1.7 g/dL when one-month interval values were used, compared to 1.1 g/dL using a 6-month interval values. Furthermore, the range of hemoglobin levels was 4.4 g/dL and 3.2 g/dL using one-month and 6-month intervals respective. Greater hemoglobin variability inversely correlated with age and serum albumin [7]. Some authors advocated the use of new algorithm that entails ESA dose adjustment only if the Hgb level fell outside the range 10.5–12.5 g/d. With this regimen, the authors claim that the proportion of patients with a hemoglobin level in the target range increased from 56% to 66% (mainly due to a reduction in the number of patients with high hemoglobin levels) with the number of ESA dose adjustment needed falling from 1/2.5 months to 1/6.1 months after 12 months [15].

Conclusion

Hgb level change was not always predictable by the ESA dose adjustment magnitude or direction.

We observed similar hematological parameters findings and IV iron usage in HD and HDF groups. However, the HD group required higher darbepoetin dose.

Similar hematological parameters findings and IV iron usage were observed in patients using Permcaths as those with native grafts. However, the Permcaths group required higher epoetin dose.

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