Hemoglobin Variability in Chronic Kidney Disease: A Cross-Sectional Study

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Abstract: *Background:* The ability to maintain dialysis patients' hemoglobin (Hgb) within narrow targets remains a significant clinical problem. This study was designed to determine the variability in Hgb values for patients with chronic kidney disease (CKD) receiving or not receiving erythropoiesis-stimulating agents (ESAs) compared with patients on dialysis receiving ESAs. *Methods:* This cross-sectional review of anemia management in CKD and dialysis patients analyzed Hgb variability by patient-year, defined as the coefficient of variability calculated for individual patients. One hundred thirty-seven CKD patient-years and 350 dialysis patient-years were available for analysis. Hgb variability was defined as the coefficient of variability calculated as the individual patient's Hgb standard deviation divided by the patient's mean Hgb times 100. *Results:* The coefficient of variability in Hgb values were significantly less in patients with CKD not treated with ESAs than in patients with CKD treated with ESAs whether they were receiving dialysis (medians: 3.96 versus 8.53%, $P < 0.05$) or not receiving dialysis (medians: 3.96 versus 7.37%, $P < 0.05$). *Conclusion:* CKD and hemodialysis patients receiving treatment with ESAs have significantly greater Hgb variability than patients with CKD not receiving ESAs. This finding suggests that the current practice pattern for the administration of exogenous ESAs is partly responsible for the observed Hgb variability.

Key Indexing Terms: Anemia management; Erythropoietin; Chronic kidney disease; Hemodialysis; ESAs. **[Am J Med Sci 2009;337(5):340–343.]**

Anemia management in patients with chronic kidney disease (CKD) on dialysis has been a focus for hemodialysis (HD) units, medical practices, and large dialysis providers for the past 10 to 15 years. Over that period of time, the average hemoglobin (Hgb) concentration in the U.S. dialysis population has progressively increased and the percentage of patients with Hgb values less than 11 g/dL (110 g/L) has decreased as a result of progressively increasing recombinant human erythropoietin (rHuEPO) doses.[1] The initial Kidney Disease Outcome Quality Initiative anemia management guidelines recommended a target Hgb of 11 to 12 g/dL (110–120 g/L), but the upper limit was increased to 13 g/dL (130 g/L) when these guidelines were revised.[2] Recently, randomized trials demonstrated possible increased mortality and no cardiovascular benefit in patients treated to target Hgb values of 13.5 g/dL (135 g/L).[3–6] These studies along with several anemia treatment trials in oncology patients prompted the Food and Drug Administration to issue a black box warning that advised against increasing Hgb values above 12 g/dL (120 g/L) using erythropoiesis-stimulating agents (ESAs).[7–9] The National Kidney Disease Outcome Quality Initiative guidelines now recommend targeting Hgb to 11 to 12 g/dL (110–120 g/L),[10] whereas the package inserts for ESAs have always recommended a target Hgb of 10 to 12 g/dL (100–120 g/L).

The discrepancy between targeted and achieved Hgb values has received little attention in clinical trials and may result, at least in part, from the artificial means employed in attempts to mimic a complex biologic system. The physiologic control of Hgb occurs on a minute-to-minute basis by regulation of erythropoietin production in response to hypoxic-inducing factor, which, in turn, regulates the number of progenitor cells progressing through the developmental pathway toward mature erythrocytes.[11,12] In dialysis patients, Hgb values are measured once or twice a month and acted upon with changes in ESA dosing. The lag time in Hgb measurement, ESA dose changes, and the net effect on erythrocyte mass along with acute events, including infections, hospitalizations, and blood loss, presumably accounts for some of the difficulty in maintaining target Hgb concentrations in patients receiving dialysis.

Studies have shown that Hgb values fluctuate over time in dialysis patients.[13] Fishbane and Berns described this phenomenon as Hgb cycling and have identified some factors that initiate and perpetuate it.[14,15] These authors reported that changes in ESA dosing, hospitalization, and changes in iron dosing were the primary factors responsible for Hgb cycling. More recently, West et al[16], using a computer curve fitting analysis confirmed marked differences in individual Hgb variability among dialysis patients. Furthermore, a recent observational study concluded that Hgb variability was independently associated with higher mortality.[17] Therefore, determining the cause of Hgb variability in this population is an important first step that may lead to better anemia management and potentially improved outcomes. However, to date, the underlying causes for the increased Hgb variability observed in end-stage renal disease has not been adequately explained.

We reasoned that if patients with CKD not on dialysis but receiving ESAs had Hgb variability similar to dialysis patients receiving ESAs, it would suggest that the need for ESAs sets into play the oscillatory cycling of Hgb. If, however, patients with CKD receiving ESAs had Hgb variability similar to patients with CKD not receiving ESAs it would suggest that events related to the dialysis treatment were primarily responsible for the observed Hgb variability. Therefore, the purpose of this study was to compare the observed variability in Hgb values in patients with CKD not receiving ESAs to the variability observed in CKD and HD patients receiving ESAs.

METHODS

Data for this study was derived from our dialysis continuous quality improvement and practice management databases. For HD patients, the study included all Hgb values from January 1, 2005 through November 30, 2006. This time period was chosen as it provided an adequate sample size and the computer algorithm used to adjust Hgb values was unchanged

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during this time period. All anemia management decisions for dialysis patients were handled through the computer algorithm that targeted a Hgb of 11 to 12.5 g/dL (110–125 g/L), increased rHuEPO if the Hgb fell below 11.1 g/dL (111 g/L), decreased rHuEPO if the Hgb increased to >12.6 g/dL (126 g/L), held the rHuEPO if the Hgb increased to >13 g/dL (130 g/L), restarted rHuEPO when the Hgb decreased to ≤13 g/dL (130 g/L), and did a number of fine adjustments based on Hgb rate of change in either direction. In general, dosing changes ranged from 10% to 40% increases or decreases depending on the Hgb change. Patients whose Hgb fell significantly below target and were on low doses of ESA were adjusted by the algorithm to 50 to 70 units per kilogram body weight instead of a percent change in dose. During this time period, all dialysis patients received intravenous rHuEPO and the algorithm consistently produced quality anemia outcomes with less than 20% of patients having Hgb values <11 g/dL (110 g/L). Hgb data were also obtained from our CKD practice management system. Because of the smaller patient pool, the time period for data extraction was from January 2002 through April 2007. Anemia in patients with CKD not on dialysis was initially treated with weekly to biweekly subcutaneous rHuEPO if the Hgb fell below 11 g/dL (110 g/L) and later with biweekly to monthly subcutaneous darbepoetin alfa. The target Hgb value for patients with CKD was 11 to12.5 g/dL (110–125 g/L). Estimated glomerular filtration rate (eGFR) was calculated from the 4 variable Modification of Diet in Renal Disease equation in patients with CKD.[18]

For analysis, Hgb variability was evaluated by calendar year. This was done to prevent decreases in eGFR from contributing significantly to Hgb variability in patients with CKD. Each individual patient's Hgb values were averaged over each year that data were available. Patient-years were then assigned to 1 of 4 groups: (1) CKD (not on dialysis) not receiving ESAs (CKD−ESA); (2) CKD (not on dialysis) receiving ESAs (CKD+ESA); (3) HD receiving ESAs (HD+ESA); and (4) HD not receiving ESAs (HD−ESA).

For dialysis patients, Hgb values obtained within 3 months of starting HD were excluded as a means of evaluating the maintenance phase of anemia management and to prevent the rise in Hgb seen at the initiation of dialysis treatment from increasing the observed variability. HD patients who did not have at least 6 monthly Hgb values recorded within a calendar year were excluded for that year. Patients with CKD not on dialysis were excluded if they did not have at least 3 Hgb values in 3 different months during the calendar year. Patients were considered to be receiving ESAs if they were administered at least 1 dose of an ESA during the months in which Hgb values were analyzed.

Finally, data from a separate short-term study of 102 HD patients receiving ESAs where Hgb values were measured on days 1, 3, and 7 were analyzed for variability to determine the reproducibility of Hgb in HD patients over a short period of time.

To determine Hgb variability, an individual patient's mean Hgb was determined for each calendar year (M_I) and the individual standard deviation (SD_I) determined. The coefficient of variation for an individual patient (CV_I) was calculated by the following formula: $CV_I = SD_I/M_I \times 100$.

Investigational/ethical review board approval was obtained with a waiver of consent for this database analysis in adherence with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects.

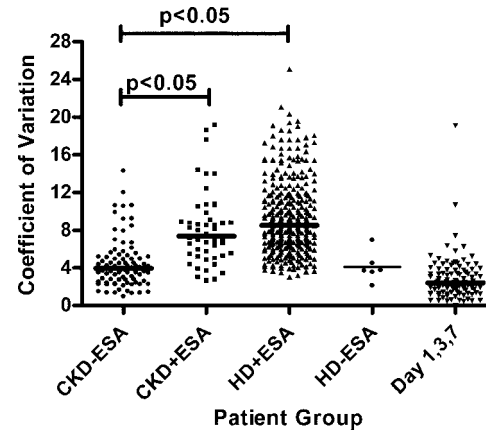

FIGURE 1. Total coefficient of variation for individual patients by groups. The horizontal lines represent the median for each group. Overall P value <0.0001. P values <0.05 for CKD−ESA versus CKD+ESA and for CKD−ESA versus HD+ESA. There was no significant difference in CV for CKD+ESA versus HD+ESA. Values for HD−ESA shown but not included in statistical analysis. Values for hemoglobin (Hgb) variability over 7 days also shown but not analyzed statistically. Shaded area represents the expected normal CV from healthy controls.[19,20]

Statistical Analysis

The CV_I for all patient groups was not normally distributed. Therefore, Kruskal-Wallis analysis for nonparametric data was used to compare groups followed by Dunn's multiple comparison test. Linear regression analysis was used to compare CV_I to eGFR and mean Hgb. All statistics were performed with GraphPad Prism version 5.0 (San Diego, CA). A P value <0.05 was considered statistically significant.

RESULTS

Ninety-two patients with CKD not on dialysis had 137 patient-years of Hgb data and 228 HD patients had 350 HD patient-years of Hgb data available for analysis. During 48 of the CKD patients-years ESAs were administered, whereas none was given in 89 patient-years. For HD patients, in 6 patient-years, ESAs were not administered and because of the small sample size these patients were excluded from the statistical analysis, although the data is shown in Figure 1. As a group, patients with CKD receiving ESAs (CKD+ESA) had a significantly greater CV_I than patients with CKD not receiving ESAs (CKD−ESA) (medians: 7.37 versus 3.96%, $P < 0.05$) (Figure 1). Dialysis patients receiving ESAs (HD+ESA) also had a CV_I that was significantly greater than patients with CKD not receiving ESAs (CKD−ESA) (medians: 8.53 versus 3.96%, $P < 0.05$) and similar to the CKD+ESA group (P = ns). Although the numbers were small, most dialysis patients not receiving ESAs (HD−ESA) had Hgb variability within the normal range. Furthermore, when measured over a short 1-week time interval, Hgb variability was within the normal range for most HD patients (Figure 1).

Within the CKD patient population there was a trend toward a progressive increase in the CV_I for Hgb as the eGFR decreased (Figure 2A), although only the slope of the line for patients with CKD not receiving ESAs (CKD−ESA) was statistically different from 0 ($P = 0.001$). For any given level of eGFR, the regression line was significantly higher (greater CV_I) for patients with CKD receiving ESAs (CKD+ESA), resulting in a significantly different y intercept ($P < 0.001$).