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Evaluation of the management of anemia in hemodialysis patients in Lebanon

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ABSTRACT

Introduction: Chronic kidney disease (CKD) patients suffer anemia as one of the major complications. Optimal therapy involves the administration and response monitoring of erythropoiesis-stimulating agents and iron therapy.
Objectives: The purpose was to assess the adherence of anemia management in end-stage renal disease to Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations. This study evaluated the impact of iron status on hemoglobin (Hb) levels, and its association with morbidity.
Patients and Methods: A prospective, multicenter, observational investigation was conducted at two hemodialysis (HD) centers over 6 months between 2013 and 2014. HD patients who aged more than 18 years without any history of active or chronic infection or cancer were enrolled. A total of 182 HD patients were included in the study.
Results: The included patients had a mean age of 57.28 years and mean Hb level of 10.29 ± 1.44 g/dL. A significant difference was noted between the prescribed and recommended doses of erythropoietin (EPO), along with that between prescribed and taken doses of EPO ($P<0.05$). A significant difference was noted between the prescribed and taken iron doses ($P<0.05$) in all months except December and April reflecting the association between the increase in Hb and adequate iron levels. Data on hospitalization was available for 78 individuals where Hb level was significantly lower in hospitalized versus non-hospitalized ones (9.92 versus 10.74 g/dL, $P=0.046$).
Conclusion: Anemia management in HD patients depends on the adherence to the KDOQI recommendations for EPO dosing and iron status management. This sheds light on the need for the implementation of strict guidelines and clinical pharmacists' involvement in HD units.

Original

Implication for health policy/practice/research/medical education:
Adherence to the KDOQI recommendations for EPO dosing and managing iron status ameliorates anemia control in hemodialysis subjects. This highlights the necessity for strict implementation of guidelines and the involvement of a clinical pharmacist in hemodialysis units.
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Introduction

Anemia is defined as hemoglobin (Hb) concentration <12 g/dL for women and <13.5 g/dL for men (1). In chronic kidney disease (CKD), normocytic normochromic anemia develops due to decreased renal production of EPO. Studies showed that the prevalence of anemia in patients with CKD is about 12% (2). Recommended target of Hb in hemodialysis (HD) patients is 11-12 g/dL (3). This should not exceed the target due to risk of hypertension, stroke, and vascular access thrombosis (4-7). Anemia management in end-stage renal disease (ESRD) is a potentially high risk and problematic challenge for both patients and health care professionals where inappropriate treatment leads to an increase in mortality and morbidity (8-10). Therefore, controlling Hb level is one of the most important factors in management of HD patients.

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Anemia treatment continues to be suboptimal in the United States as many patients did not reach target Hb due to non-adherence to prescribed regimens (44%) (11). In the Middle East region, only one study was done in Saudi Arabia in 2008 among 87 patients, which emphasizes the need for sticking to guideline protocol and evaluating causes of inadequate response (12). Absence of studies reporting pattern of anemia management in HD patients in Lebanese units leads to a gap in assessing adherence to Kidney Disease Outcomes Quality Initiative (KDOQI) guideline.

Objectives

Therefore, we aimed to assess the appropriateness of anemia management in Lebanese hospitals by comparing observed practice to KDOQI guideline recommendations. Furthermore, we evaluated the influence of iron status on Hb level, and the relationship between hemoglobin levels and morbidity.

Patients and Methods

Target population

This was a prospective, multicenter, observational investigation conducted between October 2013 and April 2014 at two HD centers in Beirut-Lebanon. Individuals were eligible to be included if they were at least 18 years of age with ESRD undergoing HD. Cancer patients on chemotherapy or radiotherapy were potentially excluded because both cancer and its treatment cause abnormalities in blood parameters that can interfere with the results (13).

Data collection was conducted in each hospital from patients' medical records (non-computerized files). Data collection sheets including demographic data, anemia parameters, lab results, treatment regimens and hospitalization rate, were filled by a pharmacist in each center. During these 7 months, laboratory values (Hb and hematocrit levels), doses of EPO and iron taken by the patient were collected monthly, and the prescribed regimens were checked also to ensure if there was any change done by the physician. Measurement levels of iron, total iron binding capacity (TIBC), transferrin saturation (TSAT), and ferritin was done every 6 months by the hospital (14). Patients who died during data collection period were included in the analysis although some data were lost.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained. The research was approved by the ethical committee of the school of pharmacy at the Lebanese International University and the hospitals where the HD units are located.

Statistical analysis

Demographic characteristics and baseline data were summarized using descriptive analysis. Categorical data were analyzed using chi-square test to determine association between Hb level and selected variables (iron status, EPO doses used). For continuous data, paired sample *t* test was used to determine any significant difference between treatment regimens. Independent sample *t* test was used for comparing mean Hb between hospitalized and non-hospitalized patients. Statistical significance was defined as $P \leq 0.05$ with two tailed tests. All analysis were conducted using the SPSS software, version 20.

Results

Demographics

Data collection conducted a total of 182 out of 189 patients (Figure 1). Results showed that percentage of males and females are approximately equal among HD patients (54.9% vs 45.1%). Hypertension was the most common co-morbidity (71.2%), followed by diabetes (42.9%). Mean age of the assessed patients was 57.28 years.

Hemoglobin level

Mean Hb for all patients was 10.29 ± 1.44 g/dL. Around 47 patients (26%) had Hb level within the target range (11-11.9 g/dL) as recommended by KDOQI guideline. December and April months scored the highest improvement in Hb level (35.1% and 34.2% respectively) among all patients (Figure 2).

Erythropoietin level

Erythropoietin (EPO) was given by subcutaneous route of administration at the end of each dialysis session which was preferential by the guideline (3,15). All these agents (epoetin alfa, epoetin beta, darbepoetin alfa, peginesatide) are equally effective (16-19). The mean EPO prescribed dose per week among all patients was 7585.8 ± 3296 IU (100 IU/kg/wk) which is approximately third of the recommended starting dose by KDOQI guideline (50-100 IU/kg three times per week). The mean EPO dose prescribed per week was significantly higher in patients

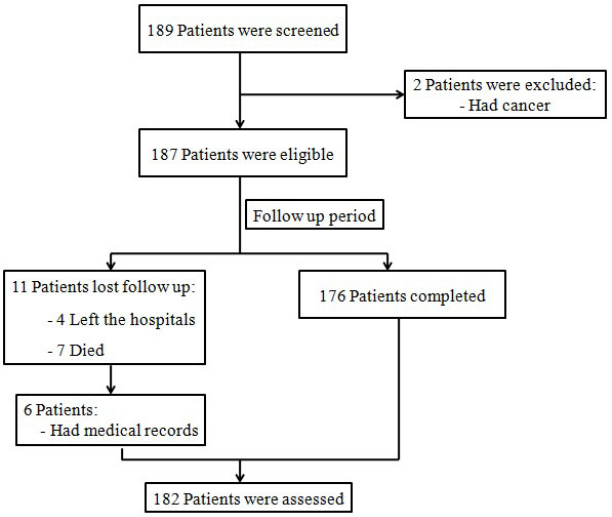

Figure 1. Enrollment and follow-up of patients in the study.

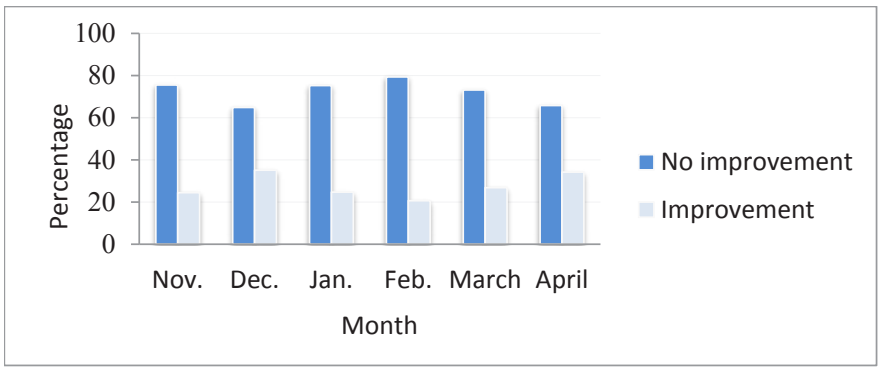

Figure 2. Percentages of hemoglobin improvement in each month.

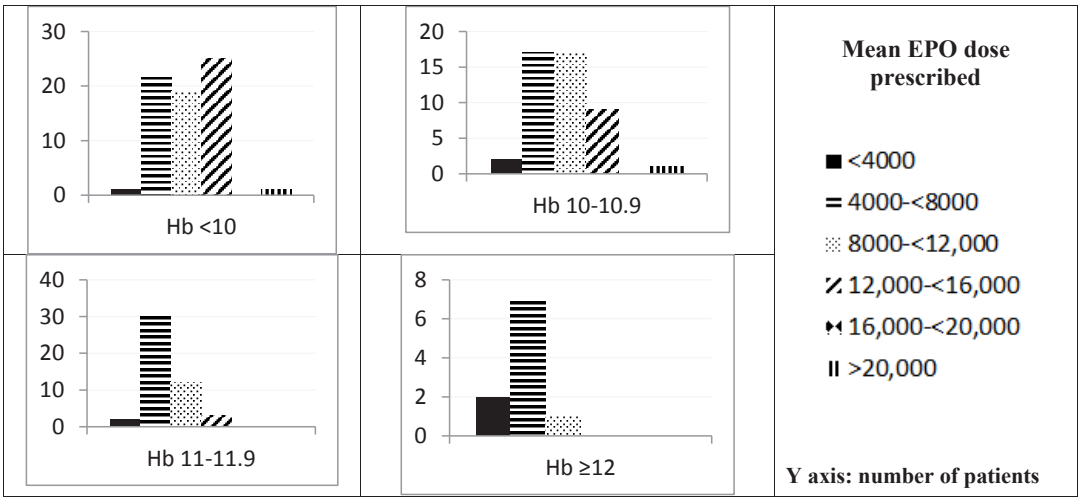

Figure 3. Relation between mean EPO dose prescribed (IU/wk) and Hb level.

with lower Hb level (Figure 3).

Results showed a significant difference between the mean of prescribed EPO doses and the mean of recommended EPO doses in all months (all *P* values were <0.05). A significant difference was shown between the mean of prescribed EPO doses and taken EPO doses in all months (all *P* values were <0.05) (Figure 4).

Iron status

Out of 182 patients, 133 received iron replacement therapy via intravenous route. IV route was preferred because it is more effective in increasing iron store than oral route (20-23). Mean difference between prescribed and taken doses of iron in all months were significantly lower than prescribed (all *P* values were < 0.05) except in two months (*P* values in December and April were 0.101 and 0.057, respectively) (Figure 5). Results showed that there was a significant difference in Hb levels between patients with different iron statuses ($P < 0.001$).

Hospitalization assessment

Hospitalization data were available for 78 patients. Myocardial infarctions (56.9%) and diabetes mellitus complications (18.2%) were the major reasons for hospital admissions (Figure 6). Mean Hb for these patients was 10.2 g/dL. Mean Hb level in hospitalized patients was significantly lower than the levels for non-hospitalized patients (9.92 versus 10.74 g/dL, $P = 0.046$) (Figure 7).

Discussion

Hb level is the most specific parameter used to establish the presence and severity of anemia in HD patients (24,25). Hematocrit level is not assessed because it is a relatively unstable parameter and lacks standardization (26). In this study the mean Hb was 10.29±1.44 g/dL. This finding was not only seen in Lebanon. A prospective observational study done in five European countries, Japan and the United States (DOPPS study), including 6069 patients showed that mean Hb levels were 10.8, 9.7 and 10.8 g/dL respectively (8).

EPO is the first line treatment of anemia in HD patients when Hb level is between 9-10 g/dL because in these patients the rate of fall of Hb is faster if untreated (27). It was found that in these Lebanese centers, higher EPO doses were prescribed for patients with lowers Hb levels. The increase in EPO dosage is not in a linear pattern

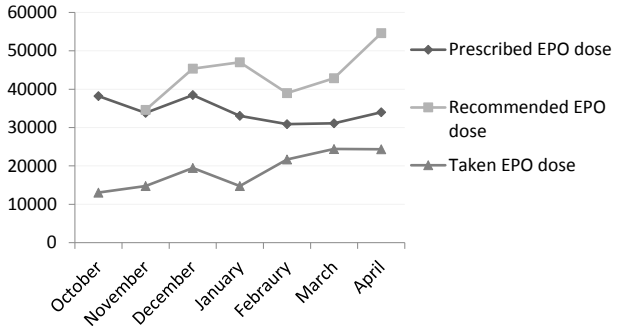

Figure 4. Comparison between prescribed, recommended and taken EPO dose.

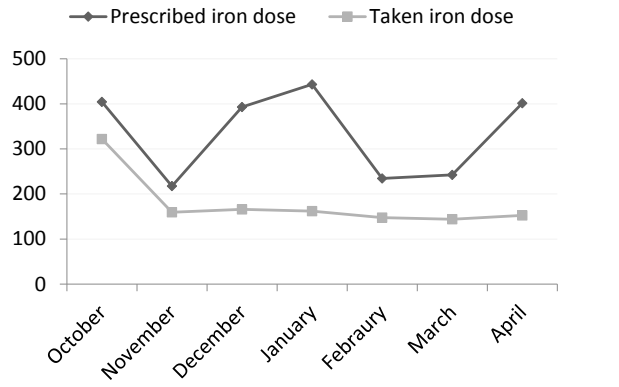

Figure 5. Comparison between prescribed and taken iron doses.

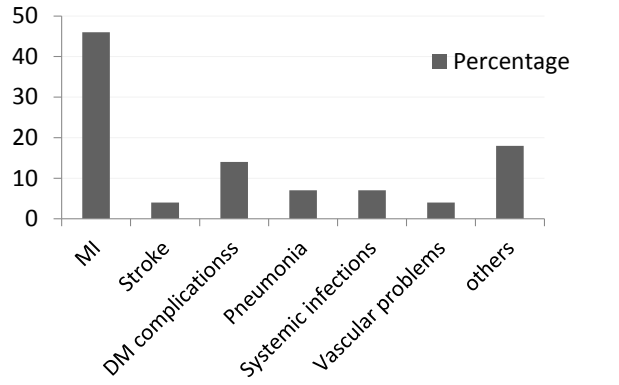

Figure 6. Reasons for hospitalization.

to achieve target Hb concentration, as observed in a similar study done in Saudi Arabia evaluating anemia management in HD patients in 2008 (25).

As shown in this study, dose adjustment of EPO depending on Hb level was not adequately done, since the prescribed doses of EPO were significantly lower than the recommended doses by KDOQI guidelines. Similarly, a study conducted in the United States revealed that not only a large difference between the actual monthly consumption of EPO (76 473 IU) and the dose recommended by KDOQI guidelines (43 500 IU) was found, but also the per-unit cost of EPO was significantly higher than that of IV iron (26).

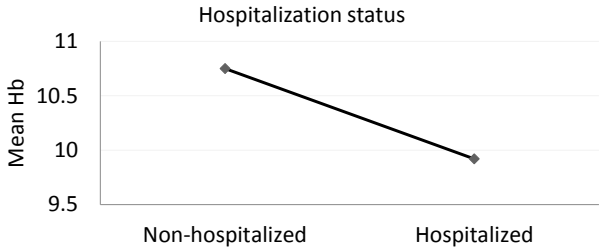

Figure 7. Association between hemoglobin level and hospitalization.

As defined by KDOQI guideline, resistance to ESA therapy is considered when there is a significant increase in the ESA dose by 50% requirement to maintain Hb level within the normal range, or a significant decrease in Hb concentration at a constant ESA dose. CKD itself is a central cause of hypo-responsiveness of ESA due to inflammatory condition that stimulates hepcidin release from the liver leading to iron deficiency (28,29). Inflammation, infection and chronic blood loss are other contributing causes (30-33). A survey done by Saudi center of organ transplant showed that 86% of physicians evaluate other causes of inadequate response to EPO therapy before increasing the doses (13,34). Thus, adequate management of iron deficiency improves anemia outcomes as shown in a randomized trial where the mean serum ferritin and TSAT prior to treatment were 235.9 ug/L and 13.5%, respectively, and both increased significantly with treatment using 250 mg of IV ferric gluconate twice monthly for 3 months (29). Mean Hb increased from 10.16 to 11.96 g/dL ($P<0.01$) and 55.3% of patients reached the target Hb of 12 g/dL.

Adherence to the prescribed iron regimens improved Hb levels as shown in both months (December and April) of this study. On the other hand, non-compliance to the EPO doses prescribed by the physician lowers the mean Hb level of the enrolled patients. Same results were shown by Chan et al where adherence to the EPO protocol was 53% and adherence to the iron protocol was 77% (35).

These findings highlight the need for implementation of clinical pharmacists in HD centers. They provide drug information on renal anemia to physicians, compile guidelines for proper use of EPO and iron in collaboration with physicians, and evaluate medication use based on laboratory data (36,37).

Both cardiovascular and diabetic complications were the most common causes of hospitalization in this study and other studies done (38-40). This was because the majority of the enrolled patients had these diseases as co-morbidities.

Moreover a study including 148 patients dialyzed in seven HD centers of Kaunas region showed that mean Hb value was 10.42 g/dL for the patients who were not hospitalized and 9.9 g/dL for the patients who were hospitalized

(P=0.02) (10).

Conclusion

Adherence to the KDOQI recommendations and management of iron deficiency improves anemia management in HD individuals. Moreover, ineffective treatment of anemia enhances risk of morbidity. Lack of patient compliance to the prescribed regimens highlights the need for involvement of clinical pharmacist in HD centers for counseling, monitoring and intervening.

Limitations of our study

There were a number of limitations in the study. Data were collected from manual medical records of the patients thus affecting its accuracy. In Lebanon, 3200 HD patients are distributed over 64 dialysis units (41). Therefore, enrollment of 182 patients from 2 HD centers in the same area is considered a small sample size.

Another limitation was that several factors alter Hb values (presence of infection, inflammatory states, blood loss, and parathyroid hormone levels) which were not evaluated as cofounders (29,42).

It would therefore be useful to conduct additional studies for evaluation of anemia treatment including HD patients in all areas of Lebanon.

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Authors' contribution

MC and MA designed the study. KS and MA generated the data collection sheet, performed the data collection, and wrote the discussion. MD and FS conducted the literature review and wrote the introduction. JS wrote the methods. MI and MC conducted the statistical analysis. KS wrote the results. All authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no points of conflicts to declare.

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Authors have nothing to disclose.

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