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PRACTICE REPORT

Appropriateness of anemia management in hemodialysis patients

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Abstract The anemia of end stage renal disease (ESRD) is common and often severe complication that can be managed successfully by erythropoiesis-stimulating agents (ESA) administration.

Aims: To investigate current practice of anemia management in hemodialysis patients and to assess the appropriateness of anemia management by comparing observed practice to the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommendations.

Settings and design: The study was conducted at two hemodialysis centers in Riyadh, Saudi Arabia. Data on anemia parameters, comorbidities, ESA dosing and iron supplementation were collected. The data were collected for 7 months retrospectively from April to the end of May 2008 and prospectively from June to October 2008. Patients who were over 18 years of age with ESRD undergoing hemodialysis were included. Patients were excluded if they have cancer or receiving chemotherapy or radiotherapy.

Results: Data were collected from 87 patients. Mean Hgb value for those patients was 11.16 ± 0.97 g/dL. Thirty-nine patients (45%) had mean Hgb values between 11.0 and 12.0 g/dL

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the target range recommended by KDOQI guideline. The mean weekly prescribed dose of erythropoietin was 8099 ± 5946 IU/Week (135 ± 99 IU/kg/Week). Information on ferritin concentrations was available for 48 (55%) patients. The mean serum ferritin concentration for those patients was 693 ± 420.5 ng/mL. Fifty-two patients had transferrin saturation (TSAT) values recorded. The mean TSAT value was 38.5 ± 19.7%. *Conclusions*: There is an opportunity to improve anemia management in hemodialysis patients particularly thorough evaluation of causes of inadequate response rate and better monitoring and management of iron status.

1. Introduction

The anemia of end stage renal disease (ESRD) is a common and often severe complication that can be managed successfully by erythropoiesis-stimulating agents (ESA) administration (Schmid et al., 2010; Dowling, 2007; Lefebvre et al., 2006; Leaf and Goldfarb, 2009).

A study screened 480 ESRD patients from six Arabian Gulf countries including Saudi Arabia (Alsuwaida et al., 2007) and found that one-third of the surveyed patients had suboptimal hemoglobin (Hgb) levels and iron stores. The limitations of this study were that it was a one day cross sectional study and the data were limited to the available information without accessing historical notes. The purpose of our study was to determine the current practice of anemia management in hemodialysis patients over seven months. Furthermore, we assessed the appropriateness of anemia management by comparing observed practice to an evidence based clinical guidelines, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and practice recommendations (National Kidney Foundation, 2007).

2. Patients and methodology

The study was conducted at two hemodialysis centers. The first is the hemodialysis center at the King Khalid University Hospital (KKUH) and the second is the Ministry of Health Centre, Prince Salman Centre for Kidney Disease (PSC), both in Riyadh, Saudi Arabia. All patients who were over 18 years of age with ESRD undergoing hemodialysis were included. Patients were excluded if they have cancer or are receiving chemotherapy or radiotherapy. Data on anemia parameters, erythropoietin dosing, iron supplementation, in addition to demographic data were collected. The data were collected over a 7 months period retrospectively from April to the end of May 2008 and prospectively from June to October 2008.

Descriptive statistics and frequency distributions were computed for all the variables. For continuous data independent samples Student's *t*-test or analysis of variance were conducted to determine any significant differences among groups as appropriate. Chi-square test was used for categorical data. Statistical significance was determined at a *p*-value lower than 0.05. All statistical analysis was performed using SPSS (version 15.00).

3. Results

3.1. Demographic and clinical characteristics of patient sample

Data were collected from 87 patients with a mean age of 50 ± 14 years. The majority of patients had been receiving hemodialysis for two or more years. The most common primary cause of end stage renal failure was diabetic nephropathy (22%). Hypertension was the most common comorbidity (76%), followed by diabetes (36%), ischemic heart disease (24%), and viral hepatitis (22%) (Table 1).

3.2. Hemoglobin level

The mean Hgb value was 11.16 ± 0.97 g/dL. Thirty-nine patients (45%) had mean Hgb values between 11.0 and 12.0 g/dL the target range recommended by KDOQI guideline. Twenty-six patients (30%) had mean Hgb values between 10.0 to 11.0 g/dL. Nine patients (10%) had mean Hgb values less than 10 g/dL. Thirteen patients (15%) exceed the recommended range (> 12 g/dL). Fig. 1 shows the distribution of patients based on Hgb values in each hemodialysis center.

3.3. Erythropoietin dose

The mean weekly prescribed dose of erythropoietin was 8099 ± 5946 IU/Week (135 ± 99 IU/kg/Week) (Table 2). The distribution of mean erythropoietin dose in hemodialysis patients from both centers is shown in Fig. 2. Fig. 3 illustrates that the erythropoietin dose decreased with increasing Hgb values. Erythropoietin was given by IV route at the end of dialysis session which is the favored route of administration in hemodialysis patients by KDOQI guideline.

3.4. Monitoring iron status

Out of 87 patients, 71 (81.6%) received iron replacement therapy all of them via the intravenous route. Information on ferritin concentrations was available for 48 (55%) patients. The mean serum ferritin concentration for those patients was 693 ± 420.5 ng/mL. Fifty-two patients had transferrin saturation (TSAT) values recorded. The mean TSAT value was 38.5 ± 19.7%. Nineteen patients had both TSAT and ferritin recorded, of them 12 (63%) were assessed as having adequate iron status, defined by KDOQI guideline as a serum ferritin concentration of ⩾200 ng/mL plus a TSAT value of ⩾20% (Table 3). Fig. 4 shows that the percentage of patients who did not meet the recommended target for transferrin saturation is higher with mean hemoglobin values < 11 g/dL. Iron status monitoring test was performed monthly in PSC and every three months in the KKUH.

3.5. Patient characteristics associated with lower hemoglobin concentrations

Factors such as albumin level and administration of intravenous iron supplementation were investigated (Table 4) and it

Table 1 Characteristic of the study patients.

Characteristic	Total (n = 87)	KKUH (n = 38)	PSC (n = 49)
Sex, n (%)			
Male	38 (44)	14 (37)	24 (49)
Female	49 (56)	24 (63)	25 (51)
Age (years)			
Mean ± SD	50.2 ± 14.3	48.76 ± 15.63	51.39 ± 13.2
Median (range)	55 (21–76)	50 (21–76)	54 (25–57)
Dry body weight (kg)			
Mean ± SD	62.6 ± 14.5	61.5263 ± 12.4	63.4913 ± 16.6
Median (range)	68 (33–101)	65.25 (39–82)	62 (33–101)
Primary renal disease, n (%)			
Diabetes nephropathy	19 (22)	6 (16)	13 (27)
Glomerulosclerosis	7 (8)	6 (16)	1 (2)
Glomerulonephritis	3 (3)	3 (8)	–
Polycystic kidney disease	4 (5)	2 (5)	2 (4)
Unknown and other	25 (29)	17 (45)	8 (16)
Not recorded	29 (33)	4 (11)	25 (51)
Duration of dialysis (year) n (%)			
0.5–0.99	20 (23)	8 (21.1)	12 (24.5)
1–1.9	31 (35.6)	10 (26.3)	21 (42.9)
⩾2	36 (41.4)	20 (52.6)	16 (32.7)
Co-morbidity, n (%)			
Diabetes	31 (36)	12 (32)	19 (39)
Hypertension	66 (76)	24 (63)	42 (86)
Ischemic heart disease	21 (24)	6 (16)	15 (31)
Hepatitis	19 (22)	5 (13)	14 (29)

KKUH = King Khalid University Hospital, PSC = Prince Salman Centre for Kidney Disease.

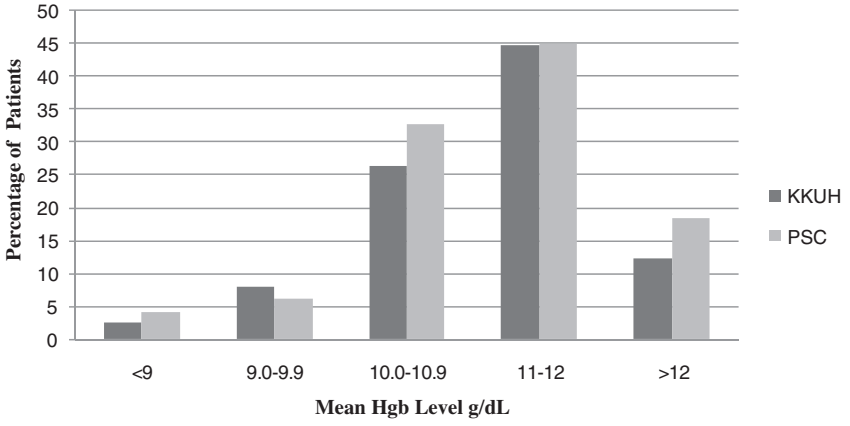

Figure 1 Percentage of patients by mean Hgb levels.

appears that females (−0.460, p = 0.04) and those with low albumin level (−0.64, p = 0.016) have statistically significant lower Hgb levels.

4. Discussion

The current study differs from the Gulf Survey on Anemia Management (GSAM 2005) study (Alsuwaida et al., 2007). GSAM 2005 was a one day survey involving 480 patients from six countries, whereas in our study data were obtained from 87 patients from one country over a period of 7 months. In both surveys the most common primary cause of end stage renal failure was diabetic nephropathy and hypertension was the common co-morbidity. Females represent 56% of our sample vs 48% in GSAM. The mean Hgb in the current study (11.16 g/dL) was slightly lower than GSAM mean of 11.45 g/dL. The percentage of patients with Hgb lower than 11 g/dL is higher in the current study (40% vs 34%), but the percentage of patients with lower than 10 mg/dL is smaller in our study (10% vs 16%). The two surveys, however, concur on an important observation that anemia is unsatisfactorily controlled in hemodialysis patients. This finding is not unique to Saudi Arabia. The European Survey of Anemia Management (ESAM) (Jacobs et al., 2005) was a one day randomized survey conducted to assess anemia management in 8100 dialysis patients from 12 countries, and demonstrated that only

Table 2 Erythropoietin dosing in the two dialysis units.

	Total (n = 87) (SD)	KKUH (n = 38)	PSC (N = 49)
Mean dose (IU/Week)	8100 (5946.5)	7755 (5930)	8367 (6006)
Mean dose (IU/g/Week)	135 (99)	127.4 (91)	141 (106)
Median dose (IU/Week)	6286	6107	6357
Median dose (IU/kg/Week)	110	99	117

KKUH = King Khalid University Hospital, PSC = Prince Salman Centre for Kidney Disease.

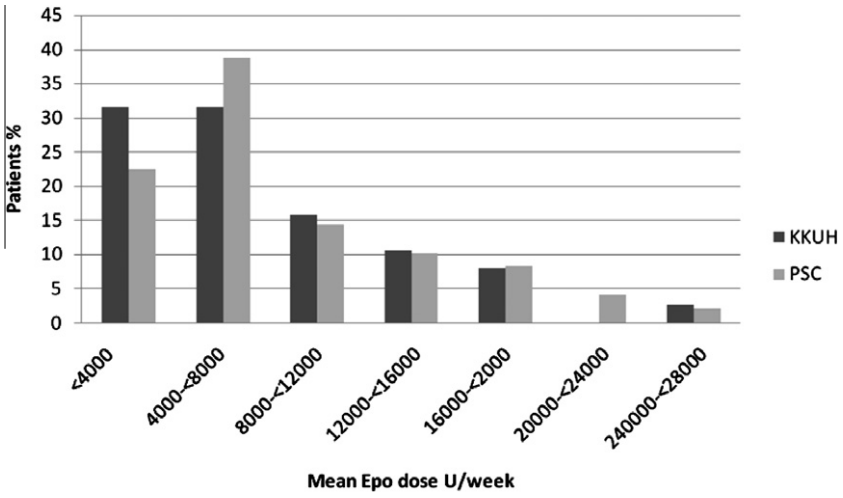

Figure 2 Distribution of weekly erythropoietin dose between the two centers.

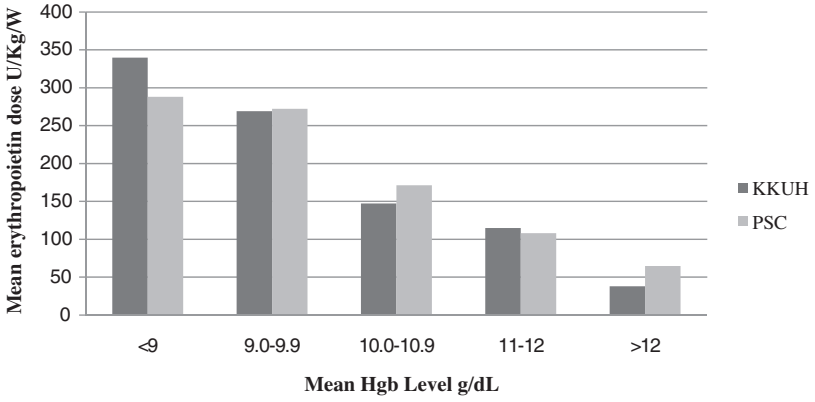

Figure 3 Mean weekly prescribed erythropoietin dose by mean Hgb level.

66% of patients achieved Hgb level >11.0 g/dL. The Dialysis Outcomes and Practice Patterns Study (DOPPS) (Locatelli et al., 2004), a prospective observational study based on the data collected from 4591 hemodialysis from five European countries, found that only 53% of the patients achieved Hgb level >11.0 g/dL.

The observed lower hemoglobin level in our study could be attributed to a number of reasons. A crucial factor for achieving a satisfactory response to erythropoietin therapy is the adequate iron status. The two primary tests used in the assessment of iron status are serum ferritin and TSAT levels. Serum ferritin concentration correlates well with total body iron stores while TSAT indicates iron supply for erythropoiesis. The accurate determination of iron status in hemodialysis patients, however, can be a challenging task. Both serum ferritin and TSAT levels may be altered by factors that are unrelated to iron metabolism. For instance, the chronic inflammatory state associated with malnutrition and clinical or subclinical infections may increase serum ferritin levels that falsely suggest a state of iron repletion (Coyne, 2006). Therefore, if ferritin levels suggest replete iron stores whereas TSAT level suggests insufficient iron availability; investigations should be done to exclude these factors. Falling to do so leads to a risk of misdiagnosing the patient with iron overload and place the patient

Table 3 Iron status in the two dialysis units using TSAT and serum ferritin level.

Iron status	Total (n = 87)	KKUH (n = 38)	PSC (n = 49)
Iron replacement (%)	71 (81.6)	31 (81.6)	40 (81.6)
IV route (%)	71 (100)	31 (100)	40 (100)
Patients with recoded ferritin	48 (55.2)	34 (89.5)	14 (28.6)
Mean ferritin level (ng/mL) (SD)	693 (420.5)	650 (336.3)	797.4 (579.5)
Patients with ferritin >200 ng/mL (%)	44 (91.7)	32 (94)	12 (85.7)
Patients with recoded TSAT (%)	52 (59.8)	7 (18.4)	45 (91.8)
Mean TSAT % (SD)	38.5 (20)	25.1 (18.7)	40.6 (19)
Patients with TSAT >20% (%)	46 (88.5)	3 (42.9)	43 (95.6)
Patients with ferritin and TSAT recorded (%)	19 (21.8)	7(18.4)	12 (24.5)
Patient with ferritin >200 ng/mL and TSAT >20% (%)	12 (63.2)	3 (42.9)	9 (75)

KKUH = King Khalid University Hospital, PSCKD = Prince Salman Centre for Kidney Disease.

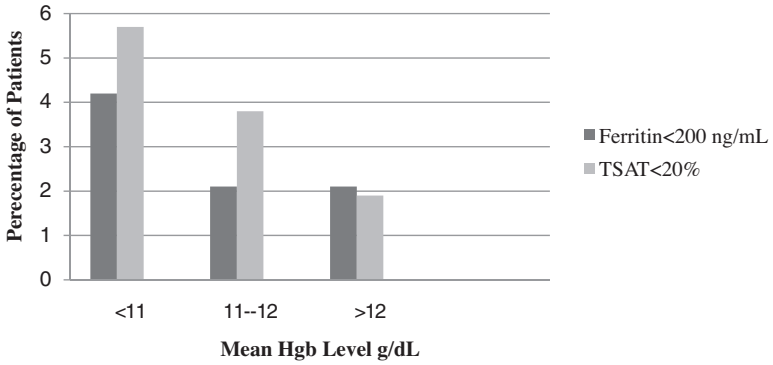

Figure 4 Iron status by mean Hgb level.

Table 4 Comparision of mean Hgb level by selected patient characteristics[a].

Characteristics	Mean HB G/DL (SD)	p-Value
Sex		
Female (n = 38)	10.95 (0.74)	0.04
Male (n = 49)	11.41 (1.17)	
Age		
18–44 (n = 31)	11.3 (0.91)	0.514
45–65 (n = 41)	11.0 (1.0)	
⩾65 (n = 15)	11.3 (0.96)	
Albumin		
<36 g/L (n = 58)	11.04 (0.85)	0.016
>36 g/L (n = 20)	11.61 (1.07)	
IV iron supplement		
No (n = 16)	11.07 (0.92)	0.688
Yes (n = 71)	11.17 (0.99)	
Duration of dialysis (year)		
0.5–0.99 (n = 20)	11.1(0.70)	0.584
1–1.99 (n = 31)	11 (1.2)	
>2 (n = 36)	11.3 (0.86)	
ACEI or/and ARB usage		
No (n = 66)	11.26 (0.95)	0.453
ACEI (n = 5)	10.85 (0.4)	
ARB (n = 10)	10.9 (1.44)	
Both (n = 5)	10.75 (0.57)	

[a] Comparison with each category was made using t-test or analysis of variance.

at risk of iron deficiency owing to inappropriate withdrawal of IV iron therapy. In our study both indices values were available for only 19 patients and of them 12 have an optimal iron status (Table 3).

As shown in Figs. 3 and 4 the erythropoietin dosage required to achieve anemia correction varies among our patients with patients with Hgb <9 g/dL receiving the highest dose of erythropoietin. Hyporesponsiveness to erythropoietin is a probable cause for the low hemoglobin level observed in some of our patients. KDOQI guidelines (National Kidney Foundation, 2007) defined the hyporesponsiveness to erythropoietin as the presence of at least one of the following: a significant increase in the erythropoietin dose requirement is needed to maintain a certain Hgb level, a significant decrease in Hgb level despite a constant erythropoietin dose, or failure to increase the Hgb level to greater than 11 g/dL despite an erythropoietin dose equivalent to erythropoietin greater than 500 IU/kg/Week. Several factors are associated with hyporesponsiveness to erythropoietin including iron deficiency, chronic blood loss, inflammation/infection, vitamin deficiencies, inadequate dialysis, hyperparathyroidism and malignancy (Kalantar-Zadeh et al., 2009; Rossert et al., 2007). Patients with inadequate response rate to erythropoietin should undergo evaluation to identify possible causes of hyporesponse to erythropoietin and iron therapy. However, this may not be always the case in practice. A survey by the Saudi Center for Organ Transplant (SCOT) on physicians' attitudes towards strategies for the treatment of anemia in patients with CKD found that 86% (115/134) would investigate the cause of inadequate response rate to erythropoietin;

however, 10% would increase the dose without further investigation of the causes of inadequate response (Souqiyyeh and Shaheen, 2007).

The percentage of patients with elevated Hgb concentrations (>12 g/dL) is lower in our study compared to GSAM (15% vs 38%). Other studies also reported a good proportion of hemodialysis patients with Hgb level >12 g/dL (Jacobs et al., 2005; Locatelli et al., 2004; Collins et al., 2005; Frankenfield and Johnson, 2002). A number of publications questioned the beneficial effects of targeting Hgb levels in excess of 12.0 g/dL (Pharommintikul et al., 2007; Singh et al., 2006; Drueke et al., 2006; Ritz et al., 2007; Pfeffer et al., 2009). A meta-analysis of nine randomized controlled trials that enrolled 5143 chronic kidney disease patients found a significantly higher risk of all-cause mortality (risk ratio 1.17, 95% CI 1.01–1.35; $p = 0.031$) arteriovenous access thrombosis (risk ratio 1.34, 95% CI 1.16–1.54; $p = 0.0001$), and poorly controlled blood pressure (risk ratio 1.27, 95% CI 1.08–1.50; $p = 0.004$) in the higher Hgb target group (12–16 g/dL) than in the lower hemoglobin target group (9–12 g/dL) (Pharommintikul et al., 2007). One possible explanation could be that dialysis patients are able to tolerate anemia at a higher degree than what would be expected and many dialysis-related factors make the delivery of oxygen to the tissues easier (Hertig and Ferrer-Marin, 2011). Other evidence also suggest that targeting hemoglobin levels in excess of 12.0 g/dL leads to small and not clinically meaningful improvements in the health related quality of life of the dialysis patients (Clement et al., 2009; Soni et al., 2010) and not cost effective (Tonelli et al., 2003). In consideration of these findings the management of anemia in the ESRD population should aim at a target Hb no higher than 10–12 g/dL.

An American study (Frankenfield and Johnson, 2002) involving 8157 hemodialysis patients found that females, blacks, patients 18–11 years old, and patients receiving hemodialysis for less than six months exhibit significantly lower hemoglobin values despite being prescribed on average, significantly higher erythropoietin doses than males, whites, older patients, and patients receiving hemodialysis for six months or more. The same study found an association between serum albumin values and prescription of IV iron and Hg values >11 g/dL. Our results show that being female and having low serum albumin concentration appears to be associated with suboptimal serum albumin concentrations (Table 4). However, our results should be interpreted with caution because of the small sample size.

There are some limitations to this study. The data collected from manual recorded patients' medical records and thus some information was missing. Several factors influencing hemoglobin values such as the presence of infection, inflammatory states, blood loss, and parathyroid hormone values were not evaluated. The small sample size is another limitation. According to SCOT there are 176 dialysis centers in Saudi Arabia catering for 10,928 patients (Anonymous, 2010). We need larger studies involving a representative sample of these centers to understand fully anemia management practices in Saudi Arabia. We need also adequately powered studies to investigate predictors of suboptimal anemia managements. The quality of life is an under researched area in Saudi Arabia and we need such local evidence to compare alternative strategies effectiveness.

In conclusion, there is opportunity to improve anemia management in hemodialysis patients particularly thorough evaluation of correctable causes of inadequate response rate and better monitoring and management of iron status.

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