Anemia and Erythropoietin Use Among Hemodialysis Chronic Kidney Disease Patients at Rumah Sakit Umum Siloam

Margaret Merlyn Tjiang[1], Elliscia Caroline[2], Jeremia Immanuel Siregar[1]

[1] Department of Internal Medicine, Faculty of Medicine, University of Pelita Harapan, Jendral Sudirman Boulevard, Lippo Karawaci, Tangerang, Indonesia 15811
[2] Faculty of Medicine, University of Pelita Harapan, Jendral Sudirman Boulevard, Lippo Karawaci, Tangerang, Indonesia 15811

Citation: Tjiang Margaret, Caroline Elliscia, Siregar Jeremia. Anemia and Erythropoietin Use Among Hemodialysis Chronic Kidney Disease Patients At Rumah Sakit Umum Siloam. Medicinus. 2024 June. 13(3): 178-184.
Keywords: Chronic kidney disease; hemodialysis; anemia; erythropoietin.
Correspondance : Margaret Merlyn Tjiang
E-mail : margaret.tjiang@uph.edu
Online First : June 2024

Abstract

Background: Chronic kidney disease (CKD) affects an estimated 8-16% of the population and is increasing in prevalence. Anemia, a common and significant complication of CKD, is primarily caused by reduced erythropoietin production, which is essential for red blood cell production. Erythropoietin, a kidney-produced hormone, stimulates bone marrow to produce red blood cells. This study examines trends in the use of erythropoiesis-stimulating agents (ESAs) and the management of anemia in dialysis CKD patients before and after the implementation of ESA reimbursemen.

Methods: This cohort study was conducted at Rumah Sakit Umum Siloam, Tangerang, Indonesia, from February to July 2017. Patients who received blood transfusions or iron supplements during the study were excluded. Data collected included age, gender, dry weight, history of diabetes mellitus, hypertension, hemodialysis adequacy, and nutritional status. Statistical analysis with a 95% confidence interval (CI) was used to assess the association between hemoglobin levels (Hb) and erythropoietin use.

Results: Sixty patients completed the study. The proportion of anemic patients (Hb <10 g/dL) increased from 22 (36.7%) to 28 (46.7%) after erythropoietin administration. A mean dose of 6000 IU/week (CI: 4679 to 7321 IU/week) was effective in achieving target hemoglobin levels, while a dose of 4131 IU/week (CI: 3479 to 4782 IU/week) was sufficient to maintain them. Additionally, a dosage of 103.31 IU/kg/week increased hemoglobin by 1 g/dL in anemic patients.

Conclusions: Erythropoietin use should be optimized given the increasing prevalence of anemia. A dosage of 103.31 IU/kg/week is recommended to achieve target hemoglobin levels, while 4131 IU/week is suggested for maintaining hemoglobin within the target range.

Introduction

Chronic kidney disease (CKD) defined as a persistent abnormality of kidney structure or function (glomerular filtration rate <60ml/min/1.73m2 or albuminuria ≥30mg per 24 hours) for more than 3 months. In the worldwide, CKD is estimated to be 8-16% and continues to grow.[1] Increase CKD remains the leading cause of morbidity and mortality especially in the elderly population. Presence of CKD increase risk of cerebrovascular disease (CVD), dyslipidemia, mineral bone disorders and anemia.[2,3]

Anemia is the most common and clinically significant complication in patients with CKD.[4] Patients in early stages of chronic kidney disease may develop

anemia and tends to worsen as progresses. Anemia is developed when the kidney loses its ability to produce the erythropoietin essential to the production of hemoglobin.[5,6] Anemia in CKD can be driven by multifactor, reduced erythropoietin production to support erythropoiesis is the primary causes. There is also the result of nutritional deficiency (iron, folic acid, and vitamin B12), diabetes mellitus, hematological disorder, advanced CKD stages, and history of hemodialysis.[7] Estimated iron losses in hemodialysis CKD patients is 1-3 gram per year, due to chronic bleeding from uremia-associated platelet dysfunction, frequent phlebotomy, and blood trappin in dialysis apparatus.[8] Anemia in CKD patients has an adverse clinical outcomes include: angina, cardiorenal anemia syndrome, cognitive impairment, left ventricle hypertrophy, higher healthcare, reduced quality of life, increased hospital admission rate, worsening CKD, accelerated progression of heart disease, and increase mortality.[9]

Erythropoietin (EPO) is a hormone produced by the kidneys that responsible to stimulate bone marrow in red blood cell production. Decreased erythropoietin in CKD linked with downregulation of hypoxia inducible factor (HIF), transcription factor for erythropoietin expression.[5] Then bone marrow does not provide enough blood cells for the body and anemia occurred.[3] The Third National Health and Nutrition Examination Survey in the USA has reported 46% men with advanced CKD had a hemoglobin (Hb) less than 12 g/dL and 21% of women had less than 11 g/dL. Intravenous injection or subcutaneous of EPO is strongly a recommended treatments because the remarkable ability to correct anemia and reduce the need to blood transfusion.[6]

Erythropoietin stimulating agents and adjuvant iron therapy are the main therapy for anemia associated with CKD. However, ESA is expensive and not limited to patients on renal replacement therapy but extended to non-dialysis patients. Recent studies have reported 20%-30% of patients received ESAs before dialysis. About 20% of dialytic patients had a Hb concentration less than 11 g/dL, whereas more than 70% of CKD patients had a Hb concentration less than 11 g/dL at the initiation of the dialysis. ESA prescription shows a significantly higher Hb concentration in patient with non-dialytic and dialytic chronic kidney disease.[4,11]

In recent decades, the treatment of anemia in patients with end-stage renal disease has aroused considerable attention, and there have been many clinical trials on the appropriate target Hb concentrations. These clinical studies raised serious concerns about intensive treatment of anemia using ESAs in patients with CKD.[12] However, little is known about the trends in the treatment of anemia with ESAs in patients with CKD that require dialysis in Indonesia. In this study, we tried to elucidate the trend of the use of ESA and anemia in dialysis CKD patients before and after the reimbursement of ESAs. This study hypothesis was ESAs usage as a maintenance in hemodialysis CKD patients especially end stage renal disease (ESRD) shown a significant increase of Hb concentration

Material And Methods

Study population

This was a cohort study at Rumah Sakit Umum Siloam, Tangerang, Indonesia. Consecutive sampling from the hemodialysis center. The study was conducted 6 months from February until July 2017. We included adult (age ≥18 yr),

dialytic CKD patients proven by laboratory and ultrasound examination that have a routine hemodialysis for at least 6 months with an estimated glomerular filtration rate less than 30mL/min/1.73m2. Patients were excluded if the Hb concentration <8g/dL at any point of enrollment, because according to hospital protocol the patients will be given blood transfusion. Patients with Hb <8g/dL at any point of the study will be excluded, because according to hospital protocol the patients will be given blood transfusion or iron supplements. Patients with other causes of anemia including active malignancy, chronic inflammatory disorder, systemic infections and active bleeding were excluded. The initial dose of ESA was administered according to manufacturer's recommendation and subsequent dosage titrated according to Hb levels so as not to exceed 12 g/dL. The following information from each patient was collected: age, gender, history of hypertension, history of diabetes mellitus, dry weight, nutritional status, and haemodialysis adequacy. Control studies was using patient CKD on hemodialysis with mild anemia with Hb concentration >10 g/dL.

Study design

We investigated baseline demographic and clinical data such as age, gender, presence of diabetes mellitus (DM), hypertension and nutritional status at the time of enrollment. Laboratory data such as Hb values were obtained at the commencement of the study, and 6 months during the follow-up period. For ESAs, we defined the doses and number of days of each prescription. Hb concentration of the patients is being evaluated and EPO administration based on Hb and dry weight of the patients.

Outcomes

This study primary outcomes were patient Hb target attainment and laboratory values. The study outcomes were Hb <10 g/dL and >12 g/dL in follow up and the Hb range 10–12 g/dL was considered the reference category. The secondary outcomes were EPO dosage for in patients anemia to reach target of the HB and the dosage for maintenance. cohort included patients from the first cohort who had transitioned to dialysis.

Statistical analysis

Using multivariable Poisson regression models with modified variances to estimate both unadjusted and adjusted prevalence ratios, along with their corresponding 95% confidence intervals (CIs). In the multivariable models, adjustments were made for age, sex, diabetes, hypertension, cerebrovascular disease, hemoglobin levels, and ESA dosage. Patient characteristics were described using means and standard deviations for numeric variables, and frequencies and percentages for categorical variables, analyzed over 6-month periods. Multivariable Pearson correlation coefficients were applied for numeric variables, while the Chi-square test was used for categorical variables. Statistical results were reported with 95% confidence intervals (CIs) and p-values, with statistical significance defined at the 0.05 level. All descriptive and multivariate analyses were conducted using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics committee

The study protocol was approved by the institutional review board (IRB) of Rumah Sakit Umum Siloam (approval number: 2017-004-01). The IRB waived the requirement for documentation of written informed consent from patients to follow up as this study was conducted by cohord. All patients provided informed consent

Result

Tabel 1 Showed that the total of 60 CKD stage V patients, with the mean age was 51.4 ± 13.3 years old. Of the 60 patients of CKD, 42 were males which are 70% and 18 were females. About half of the patients had hypertension (55%) and few had diabetes mellitus (13.3%). The mean dry weight 56.30 ± 10.59 kg and majority had good nutritional status (90%). Most patients had adequate haemodialysis (81.7%).

Table 1. Demographic of The Sample

Variables	Total (=60)	%
Age (years ± SD)	81.4 ±13.3	
Gender		
Males	42	70
Females	18	30
Other associated disease		
Hypertension	33	55
Diabetes	8	13.3
Others	19	31.7
Dry weight (kg±SD)	56.30 ± 10.59	
Nutritional status		
Good	54	90
Bad	6	10
Hemodialysis		
Adequate	49	81.7
Inadequate	11	18.3
Hemoglobin (g/dL; mean ±SD)	10.37 ± 1.12 g/dL	

The mean epo administered was 6150 ± 2279 IU/week or 113.26 ± 46.47 IU/kg/week. At the start of the study, the mean Hb was 10.37 ± 1.12 g/dL and 36.7% of the patients were anemic (Hb <10 g/dL). Throughout the study, the mean Hb was decreased slightly to 10.22 ± 0.89 g/dL and fewer patients (53.3%) were within target value (Hb ≥10 g/dL).

Table 2. The Distribution of Patients Based on Hb

Base Hb	Hb on epo	N	%
<10 g/dL	<10 g/dL	16	26.67
	≥10 g/dL	6	10.00
≥10 g/dL	<10 g/dL	12	20.00
	≥10 g/dL	26	43.33

There is evidence of negative linear association between Hb and administration of epo (r=-0.94, p<0.001).

In anemic patients, an increase in 1000 IU/week of epo decreased Hb on average by 0.36 g/dL (95% CI 0.30 to 0.43, p<0.001). Increase in 100 IU/kg/week of epo decreased Hb on average by 1.40 g/dL (95% CI 0.85 to 2.0, p<0.001). Regardless, data suggested that 103.31 IU/kg/week of epo made up for each unit of Hb deficit.

In non-anemic patients, increase in 1000 IU/week of epo decreased Hb on average by 0.41 g/dL (95% CI 0.35 to 0.46, p<0.001). Increase in 100 IU/kg/week of epo decreased Hb on average by 1.55 g/dL (95% CI 1.20 to 1.90, p<0.001). The mean epo administered for each Hb group was shown in Table 3.

Age, gender, hypertension, diabetes mellitus, dry weight, nutritional status, and haemodialysis adequacy were not correlated with Hb.

Table 3. The Mean Epo Administered in Each Hb Group

Base Hb	Hb on Epo	N	Epo (IU/week)			P value	Epo per weight (IU/kg/week)			P value
			Mean	95% CI			Mean	95% CI		
<10 g/dL	<10 g/dL	16	8700	8467	8933	p<0.001	153.31	142.17	164.45	p<0.001
	≥10 g/dL	6	6000	4679	7321		106.12	81.31	130.93	
≥10 g/dL	<10 g/dL	12	7200	6686	7714		146.01	123.37	168.66	
	≥10 g/dL	26	4131	3479	4782		75.14	61.75	88.54	

Discussion

Some studies have evaluated Hb predictors in cross-sectional designs. Early studies in Korean by Kim et al (2016) have addressed the value of treating anaemia during the transition to dialysis. The reimbursement of ESAs is associated with the increment of the prescription rate of ESAs and Hb concentration in non-dialytic CKD population.[13]

According to National Health and Nutrition Examination Survey (NHANES), a higher prevalence of anemia on CKD observed in US nursing home residents aged>64 with CKD stages 3-5. By the age 40, kidney filtration began to fall approximately 1% per year. It would lead to anemia by decreasing the production of hemoglobin. The previous study showed that there were many cases of anemia on CKD among the 50 – 59 age group where the prevalence of a rGFR of <60 ml/min/1.73 m2 was higher in the elderly compared to the young one.[14]

On the Okinawa General Health Maintenance Association (OGHMA) data, the prevalence of anemia increased as CKD progressed below an eGFR of 60 ml/min per 1.73 m^2 in both genders. The association of lower kidney function with anemia was found to be more prevalent from approximately 50 ml/min per 1.73 m^2. A previous study presented that among individuals with CKD, at all levels of GFR, anemia portended a poor prognosis and was associated with increased mortality compared to those individuals with preserved hemoglobin. The progression of anemia as the CKD stages increased can be the leading cause of death.[15]

Study that carried out by National Institute of Health (NIH), the increased CVD associated with ESRD estimated the anemia of CKD increases morbidity and mortality from cardiovascular complications (angina, left ventricular hypertrophy (LVH) and worsening heart failure), which may lead to further deterioration of renal function and the establishment of a vicious cycle termed the “cardiorenal anemia syndrome”. The presence of LVH is associated with decreased survival of patients on dialysis.[16]

In our analysis of patients an estimated 55% patients with CKD had a hypertension and 13.3% had diabetes mellitus. The mean of dry weight from patient weighted after dialysis were 56.30 ± 10.59 kg. At the start of the study 36.7% patient were anemic with Hb concentration <10g/dL and the mean of total 60 patients were 10.37 ± 1.12 g/dL.

We studied the use of Erythropoietin use as treatment of anemia in CKD patients on dialysis We found that the use of erythropoietin contributed to significantly higher Hb concentration in CKD patients on dialysis. The mean Hb concentration after being given erythropoietin, dosage of 103.31 IU/kg/week can be used in anemic patients to achieve. Erythropoietin use in patients with Hb≥ 10g/dL for maintenance has been given 4131 IU/week.

These findings are in contrast with increase Hb concentration trends in dialysis patients. Frankenfield et al, management of anemia in hemodialysis patients with end stage renal disease show the effective anemia management with the p value <0.001.[17] In this studies age, gender, hypertension, diabetes mellitus, dry weight, nutritional status, and haemodialysis adequacy were not correlated with Hb concentration. In anemic patients using EPO 1000 IU/week decrease Hb by 0.36 g/dL, increase in 100 IU/kg/week decreased Hb by 1.4g/dL. Control studies in non anemic patients

shows decrease Hb on average by 0.41g/dL and increased 100 IU/kg/week decreased Hb by 1.55 g/dL. The difference of the targeted EPO dosage to increase Hb to achieve target range were 103.31 IU/kg/week. EPO dosage to maintain Hb within target value were 4131 IU/week.

Our study has several limitations. Considering a single center-based study and the main population is rural, the result cannot be extrapolated generally to all of the population. Our study enrolled a small number of patients compared to other studies. Underlying diseases were nor included in the analysis. We suggest for the next studies to center based on more population and using more number of patients. Comorbids of the patients can be analysis to excluded other risk factor that can causes anemic.

Conclusion

Anemia is the most common complication of CKD because of reduce EPO and less production of red blood cell. Erythropoietin use could be improved considering increase prevalence of anemic patients.This study hypothesis was ESAs usage as a maintenance in hemodialysis CKD patients especially end stage renal disease (ESRD) shown an decrease of Hb concentration when EPO dosage increased in anemic patients and control studies. A dosage of 103.31 IU/kg/week might be used in anemic patients to achieve target range. A dosage of 4131 IU/week might be used to maintain Hb within target value in patients with Hb>10g/dL.

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