Kidney Res Clin Pract 34 (2015) 20–27

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

Optimal hemoglobin level for anemia treatment in a cohort of hemodialysis patients

Mi Yeon Jung [1], Soon Young Hwang [2], Yu Ah Hong [1], Su Young Oh [3], Jae Hee Seo [3], Young Mo Lee [1], Sang Won Park [1], Jung Sun Kim [1], Joon Kwang Wang [1], Jeong Yup Kim [1], Ji Eun Lee [4], Gang Jee Ko [1], Heui Jung Pyo [1], Young Joo Kwon [1,*]

[1] Division of Nephrology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[2] Department of Biostatistics, Korea University College of Medicine, Seoul, Korea
[3] Institute of Kidney Disease Research, Korea University College of Medicine, Seoul, Korea
[4] Division of Nephrology, Department of Internal Medicine, Won Kwang University College of Medicine, Iksan, Korea

Article history:
Received 28 August 2014
Received in revised form
22 November 2014
Accepted 24 November 2014
Available online 15 January 2015

Keywords:
Anemia
Hemodialysis
Hemoglobin
Mortality

Abstract

Background: Anemia is a major risk factor that contributes to mortality in patients with chronic kidney disease. There is controversy over the optimal hemoglobin (Hb) target in these patients. This study investigated the association between Hb level and mortality in a cohort of hemodialysis (HD) patients in Korea.

Methods: This study was a multicenter prospective observational study of maintenance HD patients that was performed for 5 years in western Seoul, Korea. Three hundred and sixty-two participants were enrolled. Laboratory values and mortality were accessed every 6 months. Repeated measures of laboratory values in each interval were averaged to obtain one semiannual mean value. The Hb values were divided into six groups: (1) Hb < 9 g/dL; (2) 9 g/dL ≤ Hb < 10 g/dL; (3) 10 g/dL ≤ Hb < 11 g/dL; (4) 11 g/dL ≤ Hb < 12 g/dL; (5) 12 g/dL ≤ Hb < 13 g/dL; and (6) Hb ≥ 13 g/dL. We analyzed the odds ratio for all-cause mortality, based on the Hb group, and adjusted for demographics and various laboratory values. Statistics were performed with SAS, version 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results: Mortality odds ratios relative to the reference group (10–11 g/dL) in the fully adjusted model were 3.61 for < 9 g/dL; 3.17 for 9–10 g/dL*; 4.65 for 11–12 g/dL*; 5.50 for 12–13 g/dL*; and 2.05 for ≥ 13 g/dL (* indicates $P < 0.05$).

Conclusion: In this study, a Hb level of 10–11 g/dL was associated with the lowest mortality among the groups with Hb level < 13 g/dL. Larger interventional trials are warranted to determine the optimal Hb target for Korean HD patients.

Introduction

Anemia is a common complication in patients with chronic kidney disease (CKD), particularly in hemodialysis (HD) patients. Anemia contributes to symptoms such as fatigue, dyspnea, reduced exercise tolerance, depression, and cardiovascular consequences (e.g., left ventricular hypertrophy) [1]. Anemia is also associated with increased rates of hospitalization and mortality in patients with CKD [2,3]. Many studies have shown the beneficial effects of anemia treatment such as improved quality of life; protection against cardiovascular disease [4]; and reduced mortality, morbidity, and hospitalization rates [5] in patients with

* Corresponding author. Division of Nephrology, Department of Internal Medicine, Korea University Guro Hospital, 148 Guro-dongro, Guro-gu, 152-703, Seoul, Korea
E-mail address: yjkwon@korea.ac.kr (YJ Kwon).

http://dx.doi.org/10.1016/j.krcp.2014.11.003

CKD. Until 2 decades ago, the mainstay of treatment was blood transfusion and the administration of androgenic anabolic steroids. Since the introduction of erythropoiesis-stimulating agents (ESAs) in the late 1980s, treatment modalities have undergone profound changes, which have made it possible to achieve desirable hemoglobin (Hb) levels in patients with CKD. As a result, the mean Hb and hematocrit (Hct) levels in patients with CKD, particularly patients on hemodialysis, increased steadily through 2007 in the United States [6] and through 2006 in Korea [7].

In recent decades, many observational studies and interventional trials have been performed to define the target level of Hb in patients with CKD. Several guidelines for anemia treatment from international groups and various countries have been revised for patients with CKD. However, controversy exists over the optimal level of anemia correction. In addition, there are no guidelines for the care of Korean patients with CKD—most Korean nephrologists use international guidelines, [e.g., the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines] [8] or Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [9]. The current recommended target Hb level may not optimize survival in Korean patients with CKD, particularly in patients with end-stage renal disease (ESRD).

In view of the current controversy over the target Hb level in patients with CKD and because of ethnic differences in anemia in various regions of the world, reporting results from Korean HD patients can serve as a complementary guide for clinical nephrologists and as a preliminary study for future work up. We conducted the present study, and adjusted for potential confounders and laboratory values over time, to investigate the association between Hb levels and mortality in a cohort of Korean HD patients from dialysis clinics in western Seoul.

Methods

Patients

This study was a multicenter prospective observational study of maintenance HD patients. It was performed using a cohort from 10 dialysis clinics in western Seoul between September 2006 and September 2011. We included patients who were older than 18 years and had been on HD for >3 months in September 2006. Patients with malignancies were excluded. All patients underwent conventional HD for 4 hours per session three times per week with synthetic membranes. We gathered data every 6 months for 5 years from September 2006 to September 2011. This study was approved by the Institutional Review Board of the Clinical Research Institute at Korea University Guro Hospital (Seoul, Korea). All patients provided informed consent.

Clinical assessment

We investigated baseline demographic and clinical data such as age, gender, presence of diabetes mellitus (DM), and body mass index (BMI) at the time of enrollment. Laboratory data such as Hb, iron metabolism indices (e.g., serum iron, total iron binding capacity, transferrin saturation, and serum ferritin), serum albumin, serum creatinine, serum calcium, serum phosphorus, intact parathyroid hormone (iPTH), and the single pool dialyzer clearance (Kt) per volume (V) of fluid (spKt/V) values were obtained at the commencement of the study, and then every 6 months during the follow-up period. For variables measured monthly, up to three consecutive repeated measures in each session (6-month intervals) were averaged to obtain one semiannual mean value and to mitigate the effect of short-term variations. For variables such as iPTH and spKt/V that were measured at 3-month intervals, all available repeated measures in each session were used. Each patient consequently may have had up to 10 repeated and semiannual varying values for each measure during the 5-year observation period. Observations with a missing value for any measure were excluded from the analysis. We identified patients who received kidney transplantation, changed to peritoneal dialysis, or were transferred permanently to other clinics. We included only available data from these patients.

The ESA doses were adjusted in accordance with the national reimbursement policy of health insurance in Korea, which only financially supports the use of ESAs to treat anemia in dialysis patients with a Hb level ≤ 11 g/dL [10]. All-cause mortality within a particular session was also assessed as an outcome variable.

We divided the Hb values into six groups: (1) Hb <9 g/dL; (2) 9 g/dL $\leq$ Hb <10 g/dL; (3) 10 g/dL $\leq$ Hb <11 g/dL; (4) 11 g/dL $\leq$ Hb <12 g/dL; (5) 12 g/dL $\leq$ Hb <13 g/dL; and (6) Hb ≥ 13 g/dL). A Hb level of 10–11 g/dL was the reference value.

Statistical analysis

We performed descriptive analysis to assess the baseline characteristics of the study population. All results, except for the iPTH values, are presented as the mean $\pm$ the standard deviation. Because the range of iPTH was so broad, it is presented as the median of the 25th and 75th percentile values.

The generalized estimating equation with exchangeable correlation structure was used to investigate its association between the variables and mortality because the laboratory values measured at different time points in the same person were correlated. To identify factors influencing mortality, univariate analysis was performed for each demographic and laboratory variable. Multivariate analysis was performed to calculate the odds ratio of mortality, based on the semiannual Hb level. Adjustment was performed for significant variables in univariate analysis, and performed for other variables that affect survival or the Hb level such as gender, BMI, and iron metabolism indices. Four models were examined, based on the level of multivariate adjustment: (1) the unadjusted base model (Model 1), which included Hb as the predicting variable and all-cause mortality as the outcome variable; (2) Model 2, which included adjustments for patient demographics (i.e., age, sex, presence of DM, BMI); (3) Model 3, which included adjustments for spKt/V, iron metabolism indices (i.e., ferritin, transferrin saturation), and the variables in Model 2; and (4) Model 4, which included adjustments for serum creatinine, serum albumin, serum phosphate, serum calcium-phosphorus products, and the variables in Model 3. All laboratory data were included as time-varying covariates with up to 10 semiannual averaged values per variable per patient.

All descriptive and multivariate statistics were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $P<0.05$.

Results

Study population

This study included 362 patients who were treated at 10 clinics in western Seoul in September 2004. The overall follow-up time