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Effect of Hemoglobin Target on Progression of Chronic Kidney Disease

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Abstract

Background: The introduction of erythropoietinn stimulating agent (ESA) in clinical practice has completely altered the management of patients with chronic kidney disease. However, the successful correction of anemia has not always resulted in improvement of mortality in CKD patients. One of the main reasons for failure of preservation of renal function is excessive elevation of hemoglobin (Hb) levels for CKD patients. This indicates the need for maintaining appropriate target levels of Hb to preclude the progression of CKD. The aim of this study was to compare the effects of two Hb levels on progression of CKD patients in a 2 year period.

Subjects: A total of 167 patients with chronic kidney disease (2mg <serum creatinine <8 mg/dL) and anemia (defined as Hb <10.0 g/dL) were enrolled. Eligible patients were assigned to either of two groups (a high Hb group (10-12 g/dL) or a low Hb group (8-10 g/dL)) by a computer program according to a minimization method: 1) male or female, 2) age, 3) levels of serum creatinine and 4) presence or absence of diabetes. Both groups received erythropoietin beta.

Outcomes: The primary endpoint was initiation of renal replacement therapy (RRT). The secondary endpoints were death and occurrence of cardiovascular disease (CVD).

Results: In the present study, patients whose levels of Hb were outside the target range (either over or under) for 3 successive months throughout the study were excluded. Consequently, 85 of 167 patients were eligible for analysis. A fully adjusted model of a Kaplan Meier plot of the time to initiation of dialysis is shown. Cumulative renal survival was significantly higher in the high Hb group than in the low Hb group. (HR, 1.36; 95% confidence interval; 1.04-1.79, P=0.025). Two major cardiovascular events were seen in both groups throughout the study.

Conclusion: An appropriate Hb target for prevention of progression of CKD is approximately 11 to 12 g/dL regardless of diabetes or non-diabetes.

Keywords: Chronic kidney disease; Diabetes; Renal replacement therapy

Introduction

Several large scale clinical trials [1-3] investigating the correction of anemia with a higher hemoglobin (Hb) levels (>13 g/dL) failed to show that therapy with erythropoiesis-stimulating agents (ESA) prevented the progression of renal dysfunction. Besides, one reason for failure of preservation is excessive elevation of Hb. In contrast to these demonstrations, two studies in Japan reported the renoprotective property of higher levels of Hb. Kuriyama et al. [4] reported that achieving Hb levels (11-13 g/dL) higher than the conventional target of approximately 10 g/dL with ESA prevented the progression of renal function in patients with chronic kidney disease (CKD). Tsubakihara et al. [5] recently demonstrated that maintaining higher Hb levels (11.0<Hb<13.0 g/dL) with ESA was better in preserving renal function than a low Hb levels (9.0<Hb<11.0 g/dL) in patients with CKD not on dialysis.

A similar study was performed with essentially the same findings which are described here.

Subjects and Methods

A randomized, multicenter, open-label parallel-group studies according to the principles of the Declaration of Helsinki was carried out.

A total of 167 patients with chronic kidney disease (2 mg<serum creatinine<8 mg/dL) and anemia (defined as Hb<10.0 g/dL) were enrolled. Eligible patients were assigned to either of two groups (a high Hb group (10-12 g/dL) or a low Hb group (8-10 g/dL)) by a computer program according to a minimization method: 1) male or female, 2) age, 3) levels of serum creatinine and 4) presence or absence of diabetes. Both groups received erythropoietin beta (Eposin, Cyugai Pharma, Tokyo, Japan). Duration of the study was 2 years.

Outcomes: The primary endpoint was initiation of renal replacement therapy (RRT). The secondary endpoints were death and occurrence of Cardio Vascular Disease (CVD).

Statistics

For the primary and secondary endpoints, the two groups were compared using the log-rank test and cumulative renal survival rates were estimated by the Kaplan-Meier method. The hazard ratio between the two groups was estimated using the Cox regression model, which included covariates such as age, sex and diabetes or non-diabetes, baseline Hb, serum creatinine, and estimated glomerular filtration rate (eGFR). The comparison between two groups was carried out by Wilcoxon's rank-sum test or Pearson's chi-square test.

Results

Tables 1 and 2 show the basal characteristics and laboratory

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		Group A	Group B	Group C
Sex (male/female)		41/27	62/36	0.6565
Age (years)		68.9 ± 13.6	69.7 ± 13.2	0.7446
	DM	19 (43.2%)	39 (52.0%)	0.6716
	CGN	5 (11.4%)	10 (13.3%)	
	Nephrosclerosis	8 (18.2%)	12 (16.0%)	
	others	12 (27.2%)	14 (18.7%)	

DM: diabetes mellitus, CGN: chronic glomerulonephritis; () indicates percentage.

Table 1: Basal characteristics of Patients enrolled.

	A group 68	B group 99	P values
Hb (g/dL)	9.3 ± 0.9	9.5 ± 1.0	0.3189
Ht (%)	28.2 ± 2.5	28.7 ± 3.0	0.4510
r (mg/dL)	3.35 ± 1.57	3.43 ± 1.41	0.5250
eGFR (mL/ min/1.73 m2)	16.7 ± 7.2	16.4 ± 8.1	0.5996
BUN (mg/dL)	47.2 ± 17.9	47.7 ± 16.9	0.7144

Table 2: Laboratory findings of patients enrolled.

findings of patients who were randomized and assigned into the high and low Hb groups. There were no differences between the 2 groups.

In the present study, patients whose levels of Hb were outside the target range (either over or under) for 3 successive months throughout the study were excluded. Consequently, 85 of 167 patients were eligible for analysis (Tables 3 and 4). At the time of randomization, there were no differences between the two groups in age, ratio of sex, ratio of diabetes and non-diabetes, the levels of serum creatinine and Hb. However, after excluding non-eligible patients, there were significant differences in the levels of Hb and hematocrit between the two groups, although there were no differences among the other variables. A fully adjusted Kaplan Meier plot of the time to initiation of dialysis is shown in Figure 1. Cumulative renal survival was significantly higher in the high Hb group than in the low Hb group. (HR, 1.36; 95% confidence interval; 1.04-1.79, P=0.025). In addition, all participants were graded according to the achieved Hb levels (Hb>10 g/dL or <10 g/dL) regardless of the group into which they had been assigned. Kaplan Meier plot of the time to initiation of dialysis constructed by these data also shows that cumulative renal survival was significantly higher in patients with high rather than low Hb levels (HR, 1.51; 95% confidence interval 1.06-1.74, P=0.034). Two patients were suffered from congestive heart failure and 2 patients were suffered from cerebrovascular disease. In each group, one patient was suffered from congestive heart failure and 1 patient was found to have cerebrovascular disease. There were no effects of sex, age and presence of diabetes on renal survival in both groups (data not shown). There were no significant differences in the levels and changes in blood pressure during the study period between the two groups.

Discussion

The present study demonstrated that high Hb levels prevented the initiation of dialysis therapy in patients with CKD. In previous large scale clinical trials such as CREATE (Hb levels of 13-15 g/dL) [1], CHOIE (Hb levels of 13.5 g/dL) [6] and TREAT (The Trial to Reduce Cardiovascular Events with Aransep Therapy; 12.5 g/dL) [3], no reno-protective effects of anemia correction were found. The levels of Hb were the major differences in renal protection of anemia correction in these large scale clinical studies. Our mean achieved Hb level in the high group was 11.2 g/dL, which is lower than in the three trials. Also, the levels of eGFR at the start of RRT are different. According to the United States Renal Data System [7], the mean eGFR at initiation of RRT is 11.1 mL/min/1.73 m^2. In our present study, the average eGFR was 6.5 mL/min/1.73 m^2. This difference might increase the number of patients for introduction of dialysis therapy in patients with CKD and canceled out the reno-protective effects of anemia correction. Or, the higher level of Hb might work against the prevention of progression of renal failure, since higher Hb induces more energy consumption and rapid metabolism which eventually leads to renal damage.

In the study by Tsubakihara et al. [5], the Kaplan-Meier analysis revealed no differences between the high Hb (11.0-13.0 g/dL) and low Hb (9.0-11.0) groups for the primary composite endpoints of doubling creatinine levels, initiation of dialysis, and death. However, comparing the renal survival rates using the Cox regression model showed that the risk of developing the primary endpoint was significantly lower (the risk reduction was 28%) in the high Hb than in the low Hb group. Also,

		AA group 43	B B group 42	P values
Sex (male/female)		22/21	29/13	0.0924
Age (years)		67.6 ± 13.1	68.3 ± 12.8	0.6827
	DM	17 (51.5%)	17 (48.6%)	0.9374
	CGN	4 (12.1%)	5 (14.3%)	
	Nephrosclerosis	5 (15.2%)	4 (11.4%)	
	others	7 (21.2%)	9 (25.7%)	

DM: diabetes mellitus, CGN: chronic glomerulonephritis; () indicates percentage.
AA group: patients originated from A group and the levels of Hb was not out of the initially determined range. BB group: patients originated from Bgroup and the levels of Hb was not out of the initially determined range.

Table 3: Basic Characteristics of eligible patients.

	A A group 43	B B group 42	P values
Hb (g/dL)	9.0 ± 0.9	9.8 ± 1.1	0.0016
Ht (%)	27.4 ± 2.3	29.7 ± 3.4	0.0012
Cr (mg/dL)	3.34 ± 1.55	3.27 ± 1.35	0.9335
eGFR (mL/min/1.73 m2)	16.2 ± 7.1	17.9 ± 9.6	0.5996
BUN (mg/dL)	49.6 ± 17.4	45.7 ± 17.7	0.2700

Table 4: Laboratory findings of eligible patients.

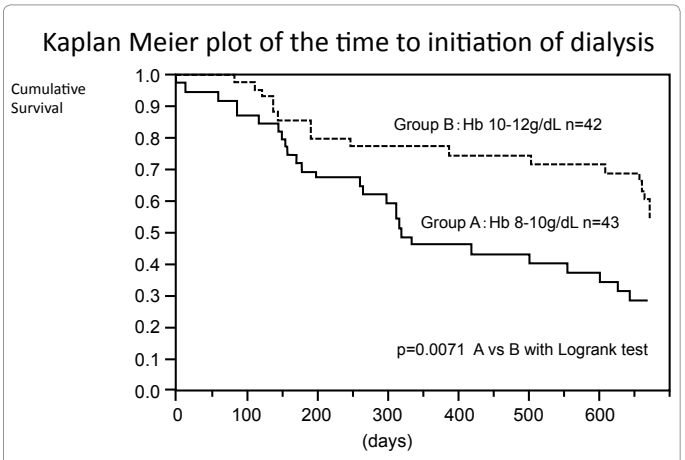

Figure 1: Kaplan-Meier plot of renal survival rates in patients with hemoglobin levels within the target range. The primary endpoint was initiation of renal replacement therapy (RRT).
Higher Hb levels significantly reduced initiation of RRT in patients on hemodialysis.

the data from the two groups comparing achieved Hb levels (Hb≥ 10 g/dL and Hb<10 g/dL) demonstrated a similar trend as found in the data obtained from the eligible patients. These values are very similar with those in our study indicating that in Japanese CKD patients, the target Hb levels are approximately 11.0-11.5 g/dL. However, it remains unclear why this level of Hb prevents the progression of CKD and emphasizes that further research is needed.

This small study has several limitations. First, the number of patients was too small to form a conclusion about the Hb levels for prevention of progression of CKD. Second, the patients enrolled in this study lived in a small area, indicating they do not represent all patients in Japan. Third, the study duration might be short and a longer period is needed to predict cardiovascular diseases. Considering these factors, a large clinical trial is needed to find the effects of correction of anemia on cardiovascular diseases in HD patients.

In conclusion, in this preliminary study, it was clearly shown that an appropriate Hb target level for prevention of progression of CKD is approximately 10 to 12 g/dL regardless of diabetes or non-diabetes.

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