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Research Article

The Effects of Heart Failure Severity on Cardio renal Anemia Treatment: A Retrospective Cohort Study

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ABSTRACT

Cardio Renal anemia syndrome is a combination of three conditions of heart failure, chronic kidney disease and anemia. Patients with this syndrome need higher doses of erythropoietin for anemia treatment. Influence of severity of heart failure on required dosage of erythropoietin in these patients is unknown. In this study, it has been investigated.In this cohort study, 108 patients with chronic renal failure who were undergoing dialysis were studied. Patients were divided into four groups based ejection fraction (EF) as normal group and mild, moderate and severe groups. Required erythropoietin dosage for treating patients' anemia in three months were recorded. Also patients' EF were measured before treatment and six months later. Mean dosage of required erythropoietin in patients with normal EF was 416.97 ± 1253.09 and in groups with mild, moderate and severe heart failure were 818.0 ± 1395.06, 563.69 ± 1524.69 and 1012.74 ± 2888.89 units respectively ($p < 0.001$). The mean EF changes within the groups were not significantly different ($p = 0.47$).In severe heart failure greater amounts of erythropoietin is needed for treating cardio renal anemia.

Keywords: Cardio Renal Anemia, Heart failure, Chronic Kidney Disease, Erythropoietin

INTRODUCTION

Cardio renal anemia syndrome as an interaction between heart failure, anemia and chronic renal disease was defined for the first time by Silverberg et al. (1 & 2). This syndrome has a cyclic nature. In other words, chronic renal disease causes anemia and heart failure. Heart failure causes anemia and renal failure. This vicious cycle exacerbates chronic renal disease, heart failure and anemia (3). Anemia is an independent risk factor for cardiovascular disease. Moreover, anemia and chronic renal disease have a synergistic effect and increase mortality rate (3-5).Cardiovascular complication is a leading cause of death in chronic renal disease. Chronic renal disease is also an independent risk factor for cardiovascular diseases. In addition, 40% of the patients with moderate to severe chronic renal failure are affected by heart failure. Furthermore, 60% of the patients with end-stage chronic renal failure are affected by heart failure. Early development of heart failure is associated with onset of anemia, which increases the risk of hospitalization due to stroke and heart failure (6).

Renal dysfunction in heart failure primarily reduces renal perfusion as a progressive dysfunction and consequently leads to venous

congestion as a retrograde dysfunction (7).Reduced renal perfusion activates renin-angiotensin-aldosterone system, which develops renal vasoconstriction. On the other hand, hypotension in heart failure patients increases renal vasoconstriction and sympathetic activity. In total, hormone-induced ischemia directly damages heart and kidney. Renal dysfunction causes salt and water retention and increases cardiac workload. Stress as a result of increased fluid retention in the heart eventually leads to left ventricular dilatation and hypertrophy, myocardial cell death and worsens heart failure (8 &9).

Given that these inflammatory conditions in cardiorenal syndrome causes anemia and resistance to erythropoietin, correction of anemia can improve prognosis of the syndrome and reduce morbidity and mortality rates in the patients. (10).Kotecha studied correction of anemia with erythropoietin in patients with cardio renal syndrome and evaluated the effect of anemia correction on prognosis of the patients. It was found out that administration of hematopoietic factors increases exercise tolerance, EF and hemoglobin and reduces hospitalization and mortality rates (11). A higher dose of erythropoietin is needed to correct anemia in patients with cardio renal anemia syndrome than patients with anemia and CKD without heart failure (12).Given the importance of correction of anemia in patients with cardio renal anemia syndrome, it is essential to determine an average weekly dose of erythropoietin for anemia treatment. So far, average weekly dose of erythropoietin based on severity of heart failure was not determined in any study. Therefore, the present study attempted to determine and examine this dose for correction of anemia.

MATERIAL & METHODS

This retrospective cohort study was conducted on 108 patients with end-stage renal disease (ESRD) undergoing hemodialysis in Akhavan Hospital in Kashan in Iran. The participants were selected from the patients with ESRD who were simultaneously at the risk of anemia. The patients were classified into four groups based on echocardiographic results. These groups were control, mild heart failure (EF> 60%), moderate heart failure (EF = 30-60%) and severe heart failure (EF<30%). Then, 27 patients were selected from each group using the patient records and the table of random numbers.

Exclusion criteria were comorbidities as valvular disease, myocardial infarction during treatment with erythropoietin, severe hypertension, any bleeding, hypothyroidism, folic acid deficiency and vitamin B12 deficiency.

Clinical and demographic data covered age, gender, weight, severity of heart failure and dose of erythropoietin for anemia treatment. This data was extracted from the patient records and was recorded in a checklist. In case of incomplete information, the patient was excluded from the study.All stages of the study were approved by the Ethics Committee of Kashan University of Medical Sciences. Ethical issues relevant to human studies were observed.The collected data was analyzed using SPSS version 19. Quantitative data was reported as mean±SD and qualitative data was reported as relative and absolute frequency. Chi-square test and one-way ANOVA were used for data analysis. Significance level (p-value) was considered less than 0.05.

RESULTS

The effect of required dose of erythropoietin for treatment of cardio renal anemia in patients under dialysis was examined in this study. The patients were divided into four groups, each group consisting of 27 individuals. Demographic data of the patients is shown in Table 1.

The average dose of erythropoietin needed to correct anemia in patients without heart failure was 1253.09 ± 416.97, in patients with mild heart failure was 1395.06 ± 818.0, in patients with moderate heart failure was 1524.69 ± 563.69 and in patients with severe heart failure was 2888.89 ± 1012.74. The difference between groups was statistically significant ($p<0.001$). Although correction of anemia increases ejection fraction in patients, the difference between groups was not

significant (p= 0.47). Contents of Table 2 show clinical results of treatment with erythropoietin.

Table 1 BaselineCharacteristics

Variables	Groups				P value
	Normal	Mild HF	Moderat HF	Sever HF	
Age	49.89±7.93	49.41±8.94	50.0±8.48	50.44±9.79	0.98
Weight	57.96±10.0	61.07±9.71	60.0±10.19	58.44±9.75	0.64
Primary hemoglobin	9.76±0.99	9.14±0.96	8.17±0.84	7.88±0.69	<0.001
Primary ejection fraction	60.18±7.53	33.33±7.34	25.55±4.0	12.96±2.5	<0.001

Table 2 Clinical Results of Treatment with Erythropoietin

Variables	Groups				P value
	Normal	Mild HF	Moderat HF	Sever HF	
Used erythropoitin	1253.09±416.97	1395.06±818.0	1524.69±563.69	2888.89±1012.74	<0.001
Final hemoglobin	12.98±0.54	12.86±0.52	12.63±0.4	12.22±0.3	<0.001
Final ejection fraction	60.18±8.7	37.04±7.63	30.92±6.36	17.78±4.0	<0.001
Ejection fraction changes	5.0±3.92	3.7±4.29	5.37±4.14	4.81±3.79	0.47

DISCUSSION

This study aimed to investigate the effect of severity of heart failure on required dose of erythropoietin for treatment of cardio renal anemia in patients undergoing dialysis. The average dose of required erythropoietin to correct anemia in patients with severe heart failure was significantly higher than other groups. No study has investigated the relationship between severity of heart failure and required dose of erythropoietin for treatment of anemia. Erythropoiesis in bone marrow in presence of either endogenous or exogenous erythropoietin stimulates hematopoiesis. This is possible in presence of several classes of cytokines such as IL-3, IL-2, IGF-1 and GM-CSF that stimulate cellular proliferation. Moreover, several proinflammatory cytokines such as IL-1, IL-6, TNF-□ and INF-□ are inhibited in hematopoiesis (13 and 14). These proinflammatory cytokines develop resistance to erythropoietin (either endogenous or exogenous). Several proinflammatory cytokines (e.g. IL-6) are independent risk factors in developing resistance to erythropoiesis-stimulating agents (15). Increased levels of these cytokines increase resistance to erythropoietin and exacerbate anemia (16). Dysfunction in erythropoiesis in chronic inflammatory conditions called anemia of chronic disorder is caused by cytokine activity and induction of resistance to erythropoietin (17). In addition to resistance to erythropoietin, increased serum levels of inflammatory cytokines inhibit release of iron from reticuloendothelial system, shorten lifetime of red blood cells and decrease production of erythropoietin. These conditions underlie anemia (18).

Congestive heart failure as a chronic inflammatory condition increases levels of proinflammatory cytokines. It is also detected that serum levels of these cytokines increase as severity of heart failure increases (19 and 20). Resistance to erythropoiesis increases as concentration of the above-mentioned inflammatory cytokines increases. Therefore, stimulation of erythropoiesis and treatment of anemia in these patients are dependent on increased level of exogenous erythropoietin. Several studies also showed anti-inflammatory effects of erythropoietin. For example, erythropoietin decreased cellular inflammatory infiltration of cells after spinal cord injury in an animal study (21-23). Therefore, erythropoiesis stimulation and anemia treatment are dependent on higher levels of erythropoietin in severe inflammatory conditions. Although evidence was not supporting, it seems that higher doses of erythropoietin for treatment of anemia in patients with severe heart failure are not limited to inflammatory conditions. Other factors such as serum albumin levels, iron reserves, adequacy of dialysis, etc. are also involved in treatment of

anemia. Further studies should be performed to investigate the effect of these factors in treatment of anemia in heart failure patients (24 & 25).

In this study, treatment of cardiorenal anemia syndrome with erythropoietin increased EF in all groups. However, no difference was found between different groups. Palazzuoli et al. studied patients suffering from cardiorenal anemia and showed that one-year treatment of patients with iron and erythropoietin improve left ventricular systolic function (26 & 27). On the contrary, Jackevicius et al. showed that treatment of cardiorenal anemia patients with erythropoietin exacerbates heart failure and increases mortality rates in a cohort study (28).

Anemia (as a common complication in congestive heart failure) exacerbates pathological condition of CHF patients. For example, one-gram per deciliter decrease in hemoglobin concentration in CHF patients increased mortality rates by 16%. It was also acknowledged that anemia significantly decreases EF (29& 30). Therefore, a part of changes in EF followed by treatment of anemia with erythropoietin is attributed to direct effects of anemia on cardiac condition. On the other hand, the effects of erythropoietin on cardiac condition should not be neglected. Various studies have shown that treatment of CHF patients with erythropoietin decrease left ventricular hypertrophy and increase EF regardless of hemoglobin correction (31 and 32).

Nephroprotective effects of erythropoietin should also be taken into account. It is acknowledged that erythropoietin has a positive effect in preventing maladaptive remodeling and fibrosis in patients with chronic renal disease. These also affected hematopoiesis even though ineffective dose of erythropoietin was administered (33 & 34). As mentioned earlier, cardiorenal anemia syndrome has a cyclical nature. Changes in either cardiac, renal or anemia condition affect other three components of this syndrome. Erythropoietin improves cardiac condition and protects the kidney through anemia correction, which moderate all three components of this syndrome and improve the patient's condition. Since cardiorenal anemia syndrome is introduced in recent decade, few studies have addressed this syndrome limited to retrospective studies. It is essential to conduct further studies (especially intervention studies) to investigate different dimensions of this syndrome and the role of erythropoietin in various components of the syndrome.

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