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Blood Count Under the Effect of Erythropoietin (EPO) in Patients with Chronic Hemodialysis

Elvedin Osmanovic[1, *], Mersiha Cerkezovic[1], Almir Jagodic[2]

[1]Hemodialysis Center, Public Health Institution Health Centre Zivinice, Bosnia and Herzegovina

[2]Department of Physical Medicine and Rehabilitation, Public Health Institution Health Center Zivinice, Bosnia and Herzegovina

Email address:

elveos@hotmail.com (E. Osmanovic)

[*]Corresponding author

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Abstract: One of the most common associated diseases in dialysis patients is anemia. The number of erythrocytes, hemoglobin and hematocrit is reduced in patients that suffer from anemia. These three measurement parameters represent the most important "red part" of the blood count. Due to renal insufficiency, patients on hemodialysis do not have enough erythropoietin, which healthy kidneys excreted, and is necessary for hematopoiesis. Erythropoietin (EPO) is the main regulator of the daily production of red blood cells. EPO that is execrated by peritubular capillary membrane cells in the kidneys circulates within plasma in order to interact with target cells in the bone marrow to maintain or stimulate erythropoiesis. The main purpose of the action of EPO is the formation of erythroid colonies. During observation of differences in the ordination of EPO in each group between men and women, there is no statistical significance evident in the incidence of anemia before and after therapy, as in p=0.70. The target concentration of hemoglobin, which must be constantly maintained in people with chronic renal anemia, is 110-120 g/l, while the target value of the number of red blood cells is 4-5x10^{12}/l and the hematocrit value is 0.35-4.5 l/l, with a slight outflow depending on the gender of the patient. The final values of the participants in our study treated with epoetin alpha show higher values of hemoglobin, hematocrit and erythrocytes, while the average values recorded in participants treated with darbepoetin decreased.

Keywords: Erythropoietin, Hemodialysis, Erythrocytes, Hemoglobin, Hematocrit

1. Introduction

One of the most common associated diseases in chronic hemodialysis patients is anemia. The number of erythrocytes, hemoglobin and hematocrit is reduced in patients that suffer from anemia. These three measurement parameters represent the most important "red part" of the blood count [2]. Due to renal insufficiency, patients on hemodialysis do not have enough erythropoietin, which healthy kidneys excreted, and is necessary for hematopoiesis. Erythropoietin (EPO) is the main regulator of the daily production of red blood cells. EPO is excreted by peritubular capillary membrane cells in the kidney, and it circulates in plasma to interact with target cells in the bone marrow to maintain or stimulate erythropoiesis. The primary goal of EPO action is the formation of an erythroid colony [13].

Anemia is still common among chronic hemodialysis patients, despite the regular use of recombinant human erythropoietin. Anemia is a common complication in patients with chronic kidney disease, which reduces their quality of life. It can sometimes be the first sign of kidney disease, but it most often occurs in the third stage of chronic renal failure, and worsens as the disease progresses [3]. Anemia requiring transfusion is characterized by erythrocyte count<2.5 million/ml blood, hemoglobin<70 g/l and hematocrit<0.2 l/l, and in these cases a blood transfusion treatment is required [14]. There are four mechanisms of anemia. The first pathophysiological mechanism is a decrease in the production of the hormone erythropoietin. Another pathophysiological mechanism is reduced red blood cell production due to inhibition of bone marrow by uremic toxins which on the one hand stop heme synthesis and on the other hand stem cell differentiation. The third mechanism involves a shortened life span of red blood cells. This

happens due to the delay of metabolic products that cause metabolic changes in the erythrocyte. Hemolysis occurs due to metabolic damage to cells [4]. The fourth mechanism includes the lack of factors necessary for hematopoiesis, and the most important of it all is iron. Anemia is twice as common in people on hemodialysis (15.4%) than in the general population (7.6%). The prevalence of anemia increased with the stage of chronic renal failure from 8.4% in stage 1 to 53.4% in stage 5, according to the results of a study in the United States [5].

Anemia leaves a mark on all organic systems, among other things, it can lead to cardiorespiratory disorders, among which there may be dyspnea, tachycardia, the possibility of heart failure, depression, impaired cognitive function, pallor of the skin, mucous membranes. It also affects the early death of hemodialysis patients [15].

2. Methods

A prospective study was conducted at the hemodialysis center, Medical Center Zivinice during period from 1 January 2021 to 31 October 2021, and the study included 57 participants of both sexes aged 18 to 80 years. It was monitored an anemic syndrome in patients on chronic hemodialysis. The parameters that are monitored include: the red part of the blood count (BC), which includes the number of red erythrocyte (Er), hemoglobin (Hb), hematocrit (Ht). Clinical symptoms present are following: general weakness, rapid fatigue, headache, pallor of the skin, palpitation, dizziness, blood pressure disorders.

Patients are divided into 4 groups:

a) The first group of participants is consisted of 15 participants that get a short-acting epoetin alpha in different doses, depending on the change in the blood count (BC).
b) The other group is consisted of 16 participants that are getting medium-length epoetin alpha at different doses depending on the variation of BC.
c) The third group is consisted of 14 participants receiving long-term epoetin beta in different doses depending on the variation of BC.
d) The fourth group is consisted of 12 participants who occasionally get epoetin alpha and darbepoetin alpha or epotin alpha and epoetin beta depending on the level of BC drop.

The study did not observe patients with acute infections, or those who replaced the central venous catheter (CVC) during the last month or constructed an arteriovenous fistula.

The aim of the paper is to study the effect of various types of erythropoietin and its doses on the red part of the blood count.

Intravenous erythropoietins are dosed in the following doses: epoetin Alpha 4000IU 2x1 per week intravenous, darbepoetin Alpha 30mg 1x1 per week epoetin beta 120mg 2x1 per month.

Target values are used for the blood parameter: erythrocytes 4-5x10^{12}/l, hematocrit 0.35-4.5 l/l, hemoglobin 110-120 g/l.

Parametric methods and tests are used to calculate statistical significance, namely: a simple T-test is used to calculate differences within groups. All erythropoietins were used for the purpose of calculating test results before and after, while the Pearson correlation test was used to calculate the correlation, where it is necessary. Statistical hypotheses were tested at the level α=0.05, that is, the difference between the groups in the sample is considered significant if $p<0.05$. Statistical analysis was carried out using the biomedical application software support program SPSS Statistics 28.0.1 and the Social Science Statistical program ©2021.

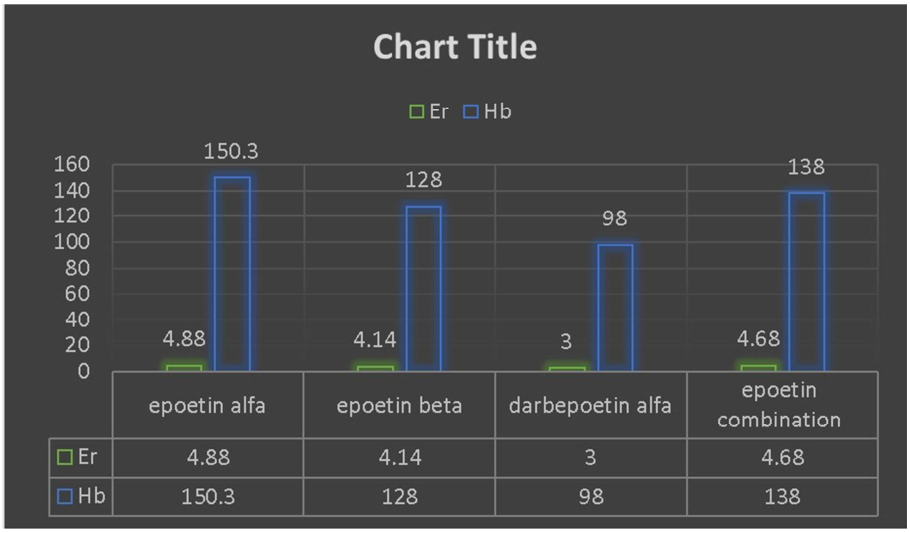

Figure 1. *The ratio of the average values of Er and Hb in various erythropoietins.*

A total of 57 participants participated in the study, consisting of 22 men (38.6%) and 25 women (61.4). This difference in the frequency of men and women was statistically significant (df=1; p=0.04). During observation of differences within each group between men and women, there is no statistical significance in the incidence of anemia before and after application of therapy where p=0.70. The average age of men is 49 years, while women is 50.8 years.

Observing all four groups of patients, it can be noticed that the average value of the number of erythrocytes (Er) and hemoglobin (Hb) differs in patients getting separate types of erythropoietin, presented in Chart 1. Epoetin alpha had the highest number of erythrocytes in patients when taking the average value for the entire group of participants (Er=4.88, Hb=150.3). Darbepoetin alpha shows poor correction of the blood count in dialysis patients, comparing the values of erythrocytes, hematocrit and hemoglobin in relation to other groups of patients (Er=3, Hb=98).

3. Results

There is also a deviation in the value of hematocrit (Htc) in all groups of patients. Epoetin alpha and the combination of epoetin obtained by the participants during the month indicate an identical hematocrit (Htc=0.44), presenting in Chart 2.

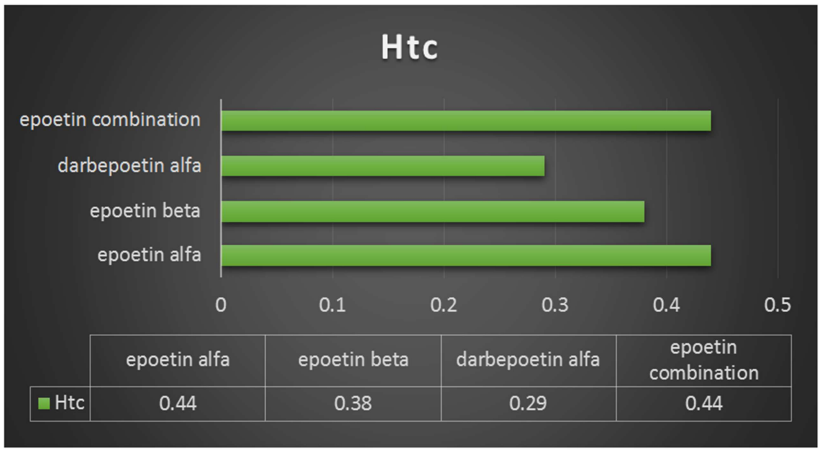

Figure 2. *The ratio of the average Htc values in various erythropoietins.*

T-test was used in all four test groups after comparing the number of red blood cells, the values of hematocrit and hemoglobin. One-sample statistical test of the tested groups showed a significant difference in erythrocyte count and hematocrit values in patients receiving epoetin alpha, epoetin beta, darbepoetin alpha and erythropoietin combination. This difference is statistically significant for the number of red blood cells, while $p<0.001$ for the hematocrit value. A slight deviation exists at the hemoglobin value, that is, a statistically significant difference in the hemoglobin value in the tested groups, $p=0.135$ (Table 1).

Table 1. *Statistically significant difference in the value of erythrocytes and germatocrit in relation to the type of erythropoietin.*

T-Test
One-Sample Statistics

	N	Mean	Std Deviation	Std Error Mean
erythrocyte count	4	4.1750	.84339	.42169
erythropoetin species	4	2.50	1.291	.645
hemoglobin values	4	466.75	691.042	345.521
hematocrit value	4	38.7500	7.08872	3.54436

One-Sample Test
Test Value=0

	t	df	Significance One-Sided p	Significance Two_Sided p	Mean Difference	95% Confidence Interval of the Difference Lower	95% Confidence Interval of the Difference Upper
erythrocyte count	9.901	3	.001	.002	4.17500	2.8330	5.517
erythropoetin species	3.873	3	.015	.030	2.500	.45	4.5
hemoglobin values	1.351	3	.135	.270	466.750	-632.85	1566.3
hematocrit value	10.933	3	<.001	.002	38.75000	27.4703	50.029

One-Sample Effect sizes

		Standardizer	Point Estimate	95% Confidence Interval of the Difference Lower	95% Confidence Interval of the Difference Lower
erythrocyte count	Cohens d	.84339	4.950	1.161	8.843
	Hedges correction	1.16554	3.582	.840	6.399
erythropoetin species	Cohens d	1.291	1.936	.146	3.672
	Hedges correction	1.784	1.401	.105	2.657

		Standardizer	Point Estimate	95% Confidence Interval of the Difference Lower	95% Confidence Interval of the Difference Lower
hemoglobin values	Cohens d	691.042	.675	-.471	1.742
	Hedges correction	955.004	.489	-.341	1.261
hematocrit value	Cohens d	7.08872	5.466	1.315	9.744
	Hedges correction	9.79645	3.9565	.951	7.051

(eritrocyte count: df=3; mean=4,17; one sided p=0,001; two sided p=0,15)
(hematocrit values: df=3, mean 38.75; Standard Deviation=0.843; one sided p<0,001; two sided p=0,02)
(hemoglobin values:: df=3, mean 466,75; one sided p=0,135; two sided p=0,270).

An additional Pearson Correlation analysis of the results was carried out, which confirms the statistical significance of erythrocyte count and hematocrit values, which is based on Fisher's Z-transformation (Table 2).

Table 2. *Analysis of Pearson correlation statistics.*

Power Analysis - Pearson Correlation

Power Analysis Table						
	N	Actual Power[b]	Assumptions Test			
			Power	Null	Alternatives	Sig.
Pearson Correlation[a]	4	.060	.05	0	.5	.05
a. Two-sided test.						
b. Based on Fischer's z-transformation and the normal displacement approach.						

The standard deviation obtained by the T-test is a measure of the scattering width of the number of erythrocyte values in relation to the average value of erythrocyte, and a standard deviation of 0.84 indicates that 68% of the participants had a number of erythrocyte close to the average value. (Table 3).

Table 3. *Standard deviation and variance around the average erythrocyte time.*

T-Test
One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
Influence of erythropoietin on erythrocyte count	4	4.1750	.84339	.42169
erythropoetin species	4	2.50	1.291	.645

(df=; 3; mean=4.17; standard deviation=0.84).

4. Discussion

Considering the issue of regulation of blood count, in erythrocyte count, hematocrit and hemoglobin values in patients with chronic renal failure, the type of erythropoietin that patients get on hemodialysis was observed. Erythropoietin as a drug for stimulating erythropoiesis is prescribed depending on the type at certain intervals. In this paper, the values of erythrocytes, hemoglobin and hematocrit in epoetin alpha, epoetin, beta, darbepopetin alpha and their combinations was analyzed [11]. The obtained results indicate that the greatest number of reduced values of erythrocytes, hemoglobin and hematocrit was observed in participants receiving darbepoetin Alpha. These participants made for 28% of all participants. The target concentration of hemoglobin, which must be constantly maintained in people with chronic renal anemia, is 110-120 g/l, while the target value of the number of red blood cells is $4\text{-}5x10^{12}$/l, and the hematocrit value is 0.35-4.5 l/l, with a slight outflow depending on the gender of the patient [6].

The authors of Gouva and co-authors researched the effects of early and delayed administration of erythropoietin therapy in predialized patients. The study showed that early initiation of treatment with epoetin alpha in patients with chronic renal insufficiency slows down the progression of the disease and delays the start of treatment by replacing kidney function [7].

Winkelmayeri W. and colleagues conducted a study according to the American Registry of Kidney Diseases. Participants were divided into two groups: those treated with epoetin alpha and those treated with darbepoetin. The average hemoglobin value in the darbepoetin group was 99 g/l with a range of 89-110 g/l, and in the epoetin alfa group the hemoglobin value was 98 g/l with a range of 88-109 g/l [8].

According to a study at the Zadar General Hospital, the average hemoglobin value in the group receiving epoetin alpha is 108.05 g/l, while the average value in the group receiving beta - erythropoietin is 107.15 g/l with a range of values of 78-127 g/L [9].

In the study of the author Carrera F. and collegues have been included 82 centers from 12 countries (Europe, Canada and Australia), participants were over ≥18 years old, and had stable chronic kidney anemia with a hemoglobin range of 110-130 g/l and were treated with regular hemodialysis. 245 participants who were treated with epoetin beta and 245 participants who were treated with darbepoetin alpha were

included in the research. The initial average values of hemoglobin in participants treated with epoetin beta were 120.9 g/l, and with darbepoetin-120.7 g/l, and, according to this study, significant differences are not observed [10].

The final values of the participants in our study who were treated with epoetin alpha show higher values of hemoglobin, hematocrit and erythrocytes, while the average values recorded in participants who were treated with darbepoetin decreased, which is common to the study conducted at Zadar Gener [12].

5. Conclusion

Chronic kidney damage is a serious public health problem, in which many complications and concomitant diseases occur. One of the most common complications is blood count disorder, that is anemia. In order to prevent anemia and, accordingly, reduce damage to blood vessels and the heart, as well as to prevent mortality, it is important to start therapy with erythropoietin, which is not excreted in sufficient quantities in chronic kidney diseases. Our research aimed to show the effect of certain types of erythropoietin because there are different types of erythropoietin available to dialysis centers.

1. On the basis of our results, we can conclude that there is a statistically significant difference in the number of erythrocytes, hemoglobin and hematocrit, when it comes to the applied types of erythropoietin. This difference is most evident in participants treated with darbepoetin alpha, who have the lowest value of the number of erythrocytes and hematocrit.
2. Participants who got epoetin alpha showed values of erythrocytes and hematocrit the highest. There was not much difference in the value of hemoglobin in these participants.
3. Anemia was not observed in any group of participants when they regularly received one of the erythropoietins.
4. Combination therapy with various types of erythropoietin gives good values for the blood counts, just as with the ordination of alpha-erythropoietin.

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