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The Frequency of Resistance to Synthetic Erythropoietin and Its Risk Factors among Chronic Hemodialysis Patients in Kerman

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Abstract

Background: The aim of this study was to determine the frequency of resistance to synthetic erythropoietin and factors affecting it among chronic hemodialysis patients in Kerman/ Iran.

Methods: This cross- sectional study was performed on chronic hemodialysis patients of three hemodialysis centers in Kerman, Iran during 3 successive months in the summer of 2016. Women with hemoglobin less than 11 and men with hemoglobin less than 12 were included in the study and using medical records, their sex, age, hemoglobin level, the amount of administered erythropoietin, tests of ferritin profile, and CPR and PTH levels were extracted and entered in a questionnaire. Patients were divided into the two groups of resistant to medication (received 300 units or more erythropoietin for each kilogram body weight in week for reaching the target hemoglobin) and the group who did not have resistance. Then, the two groups were compared in terms of mentioned factors.

Results: The frequency of resistance to synthetic erythropoietin was generally 33.66% and it was 32.4%in females and 67.6% in males that shows no significant difference between the two sexes (p=0.079). Among the studied factors, low ferritin level (P=0.012) and CRP level (p= 0.001) showed significant relationship with resistance to erythropoietin.

Conclusion: Since, iron- deficiency anemia presented with low ferritin level, and high CRP level which indicates infection and inflammation had the greatest relationship with resistance to synthetic erythropoietin, removing causes of infection and iron-deficiency anemia in hemodialysis patients in order to reduce the use of costly synthetic erythropoietin is recommended.

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Introduction

Anemia is an important problem in hemodialysis patients which is associated with high morbidity and mortality. There are many evidences which show that anemia reduces life expectancy in patients under treatment with hemodialysis, especially when hemoglobin concentration reaches less than 10 g/dm, the rate of mortality and the frequency and duration of hospitalization increase by 30% (1). There is a normochromic - normocytic anemia in most patients with chronic kidney failure (2).In case of non-treatment, it will be

associated with some physiologic disorders such as reduction of oxygen delivery to tissues and its consumption, increase of cardiac output, heart enlargement, ventricular hypertrophy, angina, congestive cardiac failure, reduction of attention-cognition, change in menstruation period and immunologic response deficiency (3). The main reason of anemia in patients with chronic kidney failure is insufficient production of erythropoietin by unhealthy kidneys. Erythropoietin is a hormone that through impact on Erythroid class of marrow causes production of red globules and hematopoiesis (4). Erythropoietin reduction following effective and functional reduction of nephrogenic mass is the most important reason of anemia in these patients. Other reasons which lead to anemia in hemodialysis patients include: shortage of B12 and folate, ferritin deficiency, chronic inflammation, severe hyper parathyroidism along with fibrosis due to it in marrow, hemoglobinopathy and shortened life of red cells in uremic conditions (5). Anemia symptoms show themselves even before beginning of uremic symptoms and appear when the rate of glomerular secretion reaches less than 30 mm/ min (6).

In all chronic hemodialysis patients, the test of complete counting of blood cells which includes hemoglobin concentration is done for examining anemia status. Anemia in chronic hemodialysis patients is defined as HB<12 mg/dl in women and HB<13 mg/dl in men. For evaluating reason of anemia in patients, complementary tests such as ferritin level, TIBC, serum ferritin level, parathyroid hormone level and CRP are performed(7). Before manufacturing erythropoietin (EPO) through recombinant method, blood transfusion was used for treating anemia. By access to synthetic erythropoietin (rhEPO), this method was replaced blood transfusion. Various studies have been performed about dose and method of medication prescription. In intravenous method, higher doses of medicine is required and in inter- peritoneal method the impact of medicine is very low (8). The most proposed method is using the medicine hypodermically. Normal dose is 50-150 IU/kg prescribed three times a week and subcutaneously (9). Following the administration of synthetic erythropoietin (rhEPO) and increasing hemoglobin, quality of life has been considerably improved (10). Erythropoietin Stimulation Agent (ESA) causes increase of hemoglobin concentration through increase of red blood cells and reduction of plasma volume through reducing activity of aldosterone- angiotensin- renin system (11). Erythropoietin Stimulation Agent recovers anemia symptoms like fatigue and asthenia and increases quality of life in hemodialysis patients. These medicines reduce the need for blood transfusion and its complications (12). Some studies show that using ESA for treating anemia and conveying HB to target hemoglobin in hemodialysis patients have been associated with improvement of heart failure symptoms and reduction of ventricular hypertrophy (13).ESA has also other functions besides hematopoietic impacts (hematic) including: protective effects on heart through oxidative stress reduction and restraining apoptosis of heart muscle cells, anti-inflammatory impacts by reducing production of inflammatory cytokines like TNF and IL6 (14). A series of complications have been reported for ESA including: hypertension (blood pressure increase), increasing the risk of thrombotic events and pure red cells aplasia (15). Despite use of recombinant human erythropoietin, still anemia is an incident finding in hemodialysis patients (16). Previous studies show that in chronic renal patients, anemia is seen in 2% of stage 2 cases, 5% of stage 3 cases,44% of stage 4 and more than 70% of

patients in stage 5.When dialysis is done, although most patients respond to ESA, 10% of patients show resistance to this class of drugs (17,18).

Resistance to synthetic erythropoietin worsens the prognosis of hemodialysis patients and increases their mortality rate. According to the recent nephrology guidelines and previous studies, the definition of resistance to synthetic erythropoietin is inability in obtaining target hemoglobin (11-12 milligram) with maximum dose of consumed erythropoietin (300 units or more for each kg of body weight in a week subcutaneously) (19). In this study, we tried to identify the factors affecting erythropoietin resistance in hemodialysis patients of three hemodialysis centers in Kerman, Iran in order to avoid excessive use of synthetic erythropoietin which is expensive and also has some side effects.

Materials and methods

This cross- sectional study was conducted on chronic hemodialysis patients in dialysis centers of Shafa, Samenolhojaj and Afzali pour hospitals in Kerman, Iran who had been treated with Erythropoietin Stimulation Agents due to anemia during summer 2016. Patients were selected through census sampling method. Hemoglobin less than 11 for women and less than 12 for men was considered as the inclusion criterion. Those who consumed immunosuppressive drugs or underwent peritoneum dialysis or had history of diseases associated with immunological deficiency (various types of hepatitis, cancer and HIV) were excluded from the study.

Through using the medical records of patients, a questionnaire was filled out for each patient by the center's nurse. The questionnaire included patient's sex, age and information about the dose of administered erythropoietin, ferritin profile and CRP and PTH level sin each month. Finally, patients were divided into the two groups of *resistant to erythropoietin* (received 300 units or more erythropoietin for each kg body weight in a week for reaching target hemoglobin) and *non-resistant*. Then, the two groups were compared with each other in relation to the mentioned factors.

The study variables were divided into the two categories of dependent and independent variables. The dependent variable which was the main variable in this study was resistance to erythropoietin which is a qualitative variable and is defined based on the need for weekly use of 300 units or more erythropoietin for achieving target hemoglobin. Independent variables were age, sex, CRP level, hyperthyroidism and ferritin level. In this study, we tried to examine the possible relationship of independent variable which was resistance to synthetic erythropoietin with independent variables and to interpret it. The studied variables have been shown in table1. Frequency, relative frequency and mean central value for descriptive statistics were used for determining factors affecting resistance to synthetic erythropoietin. First, univariable logistic regression and then multivariate, qui- square or Fisher test and independent t-test were used. Data analysis was performed through version 20 of SPSS software package.

Results

At the beginning of study, 115 patients were included in the study, but,10 patients were excluded due to noncooperation or absence at the specified time for performing tests in dialysis centers, 2 patients were excluded to undergo kidney transplantation and 2 patients died due to cardiovascular disease during the study. Finally, 101 chronic

dialysis patients with anemia (men with hemoglobin less than 12 and women with hemoglobin less than 11) were studied. Among these people, 34 patients had resistance to erythropoietin and 67 patients had no resistance and their hemoglobin had a relative increase. The frequency of resistance to synthetic erythropoietin was estimated 33% in this study.

Among 34 patients with resistance, there were 11 women (32.4%) and 23 men (67.6%) that shows no significant difference (p=0.079); therefore, in this study, sex was not considered as a risk factor for resistance to synthetic erythropoietin(table1).

Mean age of patients in the group with resistance was 61.76 ±13.60 years and in the group without resistance, it was 57.74± 13.36 years that this difference is not significant (p= 0.159). In other words, age did not have any impact on resistance to synthetic erythropoietin (table 1).

From 34 patients with resistance, in 30 patients (88.2%), ferritin level was less than 150ng/ml and they had iron deficiency and 4 patients (11.4%) had ferritin levels higher than 150ng/ml. In the group without resistance, 40 patients (59.7%) had ferritin less than 150ng/ml and 27 patients (40.3%) had ferritin more than 150ng/ml that shows significant difference (p=0.003). In other words, ferritin shortage which indicates iron deficiency was among risk factors of resistance to synthetic erythropoietin (table 1).

In the group with resistance to synthetic erythropoietin, 15 patients (44.1%) were hyperthyroidism; that is, they had PTH above 300pg/ml and 19 patients (55.9%) had PTH less than 300pg/ml. In the non-resistant group, 37 patients (55.2%) had PTH higher than 300pg/ml and 30 persons (44.8%) had PTH less than 300pg/ml that regarding P=0.291, this difference was not significant and hyperparathyroidism was not found to be related to resistance to erythropoietin (table 1).

In the group with resistance, 24 patients (70.6%) had positive CRP level and 10 patients (29.4%) had negative CRP. In the group without resistance, 17 patients (25.4%) had positive CRP and 50 patients (74.6%) had negative CRP that showed significant difference (p=0.001) and it can be concluded that positive CRP, indicating possible infection, is a risk factor for resistance to erythropoietin (table 1).

Table 2 shows the relationship of variables with resistance to erythropoietin. The results are as follows:

In relation to sex, if OR-Odds ratio for being female is considered to be 1, the variable of being male is 0.402 which is in the confidence range of 0.138-1.16 (P=0.093) that shows no significant relationship between sex and resistance to erythropoietin.

OR-Odds ratio for age was 0.982 which was in the confidence range of 0.945-1.02 and regarding P=0.4959, there was no significant relationship between age and resistance to erythropoietin.

OR-Odds ratio for iron deficiency anemia after omitting other variables was0.187 with the confidence range of 0.69-0.50 that regarding P=0.012, this difference was significant and indicated that in the present study, low ferritin was associated with resistance to erythropoietin and could be considered a risk factor for resistance.

OR-Odds ratio for positive CRP was 8.08 in the confidence rate of 2.80-23.23 that regarding P=0.001, showed significant relationship. In other words, in this study, positive CRP which shows infection was found to be related to resistance to erythropoietin and was considered as a risk factor for it.

About hyperparathyroidism in hemodialysis (PTH higher than 300), OR-Odds ratio of 0.522 in the confidence range 1.52-0.179 was obtained which is not statistically significant (P=0.2345) and indicates that high level of PTH in the blood of our subjects was not related to the received synthetic erythropoietin.

Table 1. The studied factors and estimated P value for erythropoietin resistance

Variable \ Group	resistant to erythropoietin	non-resistant to erythropoietin	Total	P value
Sex				
female	11(32.4)	34(50.7)	45(50.7)	0.079
male	23(67.6)	33(49.3)	56(55.4)	0.079
Ferritin				
>150ng/ml	4(11.8)	27(40.3)	31(30.7)	0.003
<150 ng/ml	30(88.2)	40(59.7)	70(69.3)	
PTH				
<300pg/ml	15(44.1)	37(55.2)	52(51.5)	0.079
>300 pg/ml	19(55.9)	30(44.8)	49(48.5)	
CRP				
positive	24(70.6)	17(25.4)	41(40.6)	
Negative	10(29.4)	50(74.6)	60(59.4)	0.001
Mean age(year)	61.76±13.60	57.74±13.36	_	0.159

Table 2. The relationship of variables with resistance to erythropoietin

Variable	OR	p.v	CI
Age (year)	0.982	0.351	1.02-0.945
sex(femal /male)	0.402	0.093	1.16-0.138
ferritin (ng/ml)	0.187	0.012	0.69-0.050
CRP(mg/l)	8.08	0.001	23.23-2.80
PTHpg/ml)	0.522	0.235	1.52-0.179

Discussion and conclusion

Reduction of erythropoietin is one of the most important reasons of anemia in end stage renal disease (ESRD) patients. Using erythropoietin stimulation agent has not led to anemia recovery and reducing its complications and the need to blood transfusion in these patients. There are still 10% of ESRD patients who do not respond to these medications appropriately. The most prevalent reasons of non-response to erythropoietin stimulation agent are iron deficiency anemia, infection and inflammation, PTH higher than 300pg/ml (hyperthyroidism), hemoglobinopathy and using anti-hypertensive drugs thatinhibit angiotensin II(20).

The results of our study showed that sex, in case of omitting other confounding factors, does not have any relationship with resistance to erythropoietin (P= 0.093).

While, other studies have shown that resistance to erythropoietin is seen more among young women. In 2004, a study was conducted by Dilorio et.al on 3224 chronic hemodialysis patients in which women in the age group of 22-45 years old needed more erythropoietin for achieving target hemoglobin comparing men. In the mentioned study, the reason of more need for drug was as attributed to iron deficiency status due to menstruation bleeding in women (21).

In a study conducted by Doquin Hong in 2015, 310 hemodialysis patients (163 men and 147 women) were examined in regard to the amount of erythropoietin used for

correcting hemoglobin level. Erythropoietin resistance index (ERI) in women was higher than men and being female was recognized as a risk factor for erythropoietin resistance (22).

In another study conducted in 2015 by Michelle Teadoro et.al on factors affecting synthetic erythropoietin resistance, sex was not introduced as an effective factor in resistance to erythropoietin (23) which is consistent with our finding.

The reason that in some studies, female sex has been considered as a risk factor for resistance to erythropoietin is iron deficiency anemia due to monthly menstruation and testosterone shortage in women. In our study, 34 patients showed resistance of whom, 11 patients were female. Therefore, regarding small number of patients with resistance, finding role of sex is not accurate and requires a greater statistical population.

In the present study there was no significant difference between the mean age of the resistant group and non-resistant group (P=0.159) that shows age does not have any impact on resistance to synthetic erythropoietin. This finding is consistent with the results of most studies on resistance factors (7). A cohort study was performed by Bamgbloa et.al in 2009 on the required dose of erythropoietin in hemodialysis patients in two age groups of children and adults. Though, previous notion was that adolescents and children, due to the ability of hematopoiesis out of marrow, show better response to hematopoiesis stimulation agents, in the mentioned study, results were different and response of adolescent group to drug was weaker and the dose of consumed erythropoietin was higher; in other words, resistance to hematopoiesis stimulation agents was higher in the group of 8 to 20 years and its reasons were considered weak nutrition status, irregular dialysis, infection and inflammation that all of them are more probable in children. Of course, it should be mentioned that in this study age and sex, alone, were not in trod used as strong predicting factors for resistance to drug (24).

In the present study, ferritin level of less than 150mg/dl which indicates shortage of iron storages had a significant relationship with resistance to erythropoietin (P=0.012). In most studies, low ferritin level and iron deficiency anemia are among reasons of resistance to hematopoiesis stimulation drugs (25-27) which is consistent with our results.

According to the studies performed by Besarab et al. andLiet al. on the effectiveness of using synthetic erythropoietin for compensating anemia in hemodialysis patients, alternative evaluation of saturation percent and serum ferritin concentration is necessary and if serum ferritin is lower than 100 mg/dl and iron saturation percent is less than 20%, desirable response will notbe obtained following injection of synthetic erythropoietin (28, 29).

In the present study, ferritin shortage disrupted suitable response to synthetic erythropoietin. Since our patients with iron deficiency anemia and ferritin shortage in previous months had received injective ferritin, it seems that iron replacement had not been performed completely and a more accurate survey should be performed to determine iron deficiency reasons and non- compensation of ferritin after receiving injective iron (Venofer).

According to the results of our study, hyperthyroidism (PTH level higher than 300pg/ml in hemodialysis patients) does not have any relationship with resistance to synthetic erythropoietin, while, in other studies, hyperthyroidism has been regarded as a risk factor for resistance to synthetic erythropoietin. In a study conducted by Chang- Liang et.al, 37 patients who had PTH>300pg/ml were examined during a 3-

month period before and after parathyroidoctomy in terms of required dose of erythropoietin for marinating hemoglobin in the range of 11-12. It was shown that hyper parathyroid treatment and PTH preservation between 150 to 300pg/ml considerably reduces the need to erythropoietin for correcting anemia (30). In a study conducted by Rao et.al, 18 hemodialysis patients were examined for 1 to 3 years for synthetic erythropoietin dose and PTH level. The rate of erythropoietin required for maintaining hemoglobin in target range in the group with high PTH (7 persons) was very higher than that in the other group. All patients in this study underwent marrow biopsy. In the group with high parathyroid hormone level, the degree of marrow fibrosis was clearly higher than the group with appropriate response (31). It seems that the reason of difference of our results with the results of other studies is small number of hemodialysis patients with PTH above 300pg/ml (15 patients) in the drug- resistant group and short period of study (only 3 months).

In the present study, positive CRP level hada significant relationship with resistance to synthetic erythropoietin (P=0.001) which is consistent with the results of most of previous studies. In a study conducted by Panichi et.al in 2011, the relationship of CRP and IL6 level with resistance toEprex was assessed and it was observed that resistance to erythropoietin stimulation agents had a significant relationship with CRP level above 30 and IL6 and the rate of cardiovascular incidents was reported more in the group with resistance to synthetic erythropoietin comparing to the other group (32). In the study of El-KhatinetAl., the relationship between high CRP level and resistance to synthetic erythropoietin was reported. The amount of erythropoietin required for maintaining hemoglobin in the range of 11-12 was clearly more in the group with CRP above 5 (33).

In the Nand et al. study, high CRP was introduced as a criterion of infection and inflammation and it had a completely significant relationship with resistance to synthetic erythropoietin (34). In another study conducted by BaranietAl., 30 hemodialysis patients with target hemoglobin of 12 were followed up during 6 months in terms of erythropoietin dose and CRP level. The results of this study showed that the rate of consumed erythropoietin required for maintaining hemoglobin in level 12 in the group with CRP above 20 mg/dl, was80% more than that in the group with low CRP (35).

In the present study, high CRP level which indicates infection and inflammation had a certain relationship with resistance to synthetic erythropoietin. It seems that in our patients, the most reasons of positive CRP were pneumonia, infection of dialysis Cather and urinary infection.

Suggestions

Since it was shown in the present study that infection and inflammation (high CRP level) and iron deficiency anemia (low ferritin) are effective factors in lack of appropriate response to synthetic erythropoietin, it is suggested to remove infection in patients, identify reasons leading to iron deficiency (hemolysis, digestive bleeding, …) and treatiron deficiency anemia in order to reduce the required dose of synthetic erythropoietin which is costly and is sometimes associated with some complications.

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