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Original Article

SERUM ERYTHROPOIETIN IN PATIENTS WITH CHRONIC RENAL FAILURE IN THE PREDIALYSIS STAGE

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Summary

A prospective study was carried out of serum erythropoietin levels in patients with chronic renal failure/chronic kidney disease in the predialysis period. The study is part of scientific project № 2/2022, financed by Medical University-Pleven. Fifty patients were tested – 22 males and 28 females (average age 63.7±13.0), with average serum creatinine 253±127 mcmol/l and average glomerular filtration rate of 22.6±11.8 ml/min/1,72 m2. The results showed that the serum erythropoietin level varied from 1.86 to 48.50 U/l and was below the borderline in only three patients. There were no significant differences between serum erythropoietin and haemoglobin values in both genders. No differences were found between the average haemoglobin values of patients with different values of serum erythropoietin. Non-significant differences were found in the values of serum erythropoietin in patients with different haemoglobin values. A statistically significant difference between the average value of serum erythropoietin was seen in the group of patients who were not undergoing treatment for anaemia with recombinant erythropoietin (8.5±5.9 U/l) and the groups treated with a dose above 3000 UI/weakly (from 18.6±11.3 to 19.7±8.8 U/l).

Keywords: erythropoietin, chronic renal failure, renal anaemia, predialysis

Introduction

Chronic renal failure (CRF) has recently been defined as a medical problem of paramount social and economic significance [1, 2]. The incidence of CRF in the 1980s varied from 100 to 300 per 1 million population, but nowadays, it is over 1000 per million. The most common complication of CRF is renal anaemia, which develops due to reduced production of erythropoietin from the kidneys [3].

The National Health and Nutrition Examination Survey III summarises collected data for the period 2007-2010 and proves that anaemia is two times more common in chronic kidney disease (CKD) (15.4%) compared to

the general population (7.6%). The frequency increases from 8.4% in CKD stage I to 53.4% in CKD stage V [4].

Anaemia continues to be a significant complication in patients with CRF/CKD, even though it can be treated [3]. It increases cardiovascular risk and reduces life expectancy [2].

Since the discovery of erythropoietin in 1977 [5] and the cloning of the gene responsible for its synthesis in 1985 [6], human recombinant erythropoietin has begun. It has been widely used for renal anaemia (RA) treatment in patients in both dialysis and predialysis stage of CRF/CKD.

Many publications are connected to the treatment of RA with recombinant erythropoietin. However, only some of them have focused on measuring serum erythropoietin in patients with CRF/CKD.

Materials and Methods

Fifty patients with CKD stage 2-4, monitored and receiving conservative treatment for RA, were studied. Male patients were 22 (44.0%) at an estimated average age of 63.7±13.0 years, and females were 28 (56.0%) at an estimated average age of 68.3±10.9 years.

Standard laboratory markers were used, and creatinine clearance (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formulas. Serum erythropoietin levels were tested using a solid phase, enzyme-linked chemiluminescent immunometric test with IMMULITE 2000 Immunoassay System – Siemens Healthineers. Reference ranges of serum erythropoietin are from 4.2 to 20.8 mU/ml. The results were evaluated with alternative and variational methods of statistical analysis.

The study is part of scientific project № 2/2022, financed by Medical University-Pleven and approved by the University ethics committee.

Results

The average values of haemoglobin, serum iron and transferrin saturation showed insignificant differences in patients of both genders. The average values of serum creatinine and creatinine clearance were with minor, inconsequential differences in patients of both genders ($p>0.1$) (Table 1).

The average value of serum erythropoietin was 14.9±10.2 mU/ml, in males – 17.6±11.2 mU/ml, in females – 12.9±8.9 mU/ml, the difference was insignificant ($p>0.1$).

The serum erythropoietin level in the studied patients varied widely – between 1.86 and 48.50 U/l. Three patients (6%) had levels lower than the borderline. In many patients – 23/47, the value of serum erythropoietin was in the lower half of the normal range, and in 14/47, it was above the upper limit of this interval. The analysis of the serum erythropoietin and the haemoglobin values showed that the severity of anaemia was equal in all three groups based on the erythropoietin values. The average haemoglobin value was even lower in the group

Table 1. Main laboratory markers, characterizing the severity of anemia and the stage of CKD (n=50).

	Haemoglobin (g/l)	Serum iron (mcmol/l)	TSAT (%)	Serum creatinine (mcmol/l)	Creatinine clearance (ml/min/1,72m2)
Male	110.0±17.3	12.4±5.4	24.7±8.7	240±112	26.4±13.6
Female	110.5±13.5	12.4±5.3	23.0±9.6	262±140	19.5±9.3
All	110.3±15.1	12.4±5.3	23.8±9.1	253±127	22.6±11.8

Table 2. Average values of haemoglobin, serum creatinine and creatinine clearance in different levels of serum erythropoietin (n=47).

Serum erythropoietin (UI)	Number of patients	Haemoglobin (g/l)	Serum creatinine (mcmol/l)	Creatinine clearance (ml/min/1,72m2)
4.2-12.5	23	111.1±17.5	243±119	23.5±13.1
12.6-20.8	10	111.3±16.5	243±90	21.3±8.2
Above 20.8	14	108.3±11.3	266±154	22.2±11.9

with the highest erythropoietin levels. Still, the difference in the values in the other two groups was insignificant (p>0.1). The average values of serum iron, transferrin saturation, serum creatinine and creatinine clearance showed that iron metabolism and severity of CKD were equal in patients with different values of serum erythropoietin (Table 2).

The value of haemoglobin in tested patients varied from 72 to 131 g/l. A comparison between the average serum erythropoietin levels in the groups with different haemoglobin levels did not find a relation between both laboratory markers. (Table 3) Even in patients with the most severe anaemia, the average serum erythropoietin level was higher than those with milder anaemia.

Treatment of anaemia with recombinant erythropoietin was administered to 37 of the 50 patients tested. The analysis of the connection between levels of serum erythropoietin and the dose of recombinant erythropoietin showed that the average value of serum erythropoietin was the lowest in patients who did not receive recombinant erythropoietin (Table 4). The difference in the levels of serum erythropoietin in patients treated with recombinant erythropoietin in doses from 500 to 2000 UI/week was insignificant (p>0.1). Still, the difference in serum erythropoietin levels in the groups treated with more than 3000 UI/week was significant (p<0.05). A gradual increase in the average serum erythropoietin level with the rise in the dose of exogenous erythropoietin applied for treatment was determined (Table 4).

A gradual increase in the average haemoglobin level was noticed with increasing the erythropoietin dose. The difference was significant (p<0.05) only between the average haemoglobin levels in untreated patients and those treated with recombinant erythropoietin with a weekly dose of 3000 to 4000 UI. It was also noted that the average haemoglobin value was lower in the group with doses from 6000 to 9000 UI/weekly. Such values are unsurprising because these patients were in the correctional phase of renal anaemia treatment, lasting below six months (Table 4).

Data analysis of the distribution of patients in four groups based on the severity of CRF, determined by the serum creatinine level, showed similar levels of serum erythropoietin in all groups. Comparisons showed only slight dissimilarities (p>0.1). (Table 5)There were no significant differences in haemoglobin values and doses of recombinant erythropoietin between the different groups (p>0.1).

The summary of results allows us to make several conclusions. Firstly, there were no differences between the average levels of serum erythropoietin, haemoglobin, parameters of iron metabolism and stage of CKD in patients of different genders. The serum erythropoietin level in most patients was not lower; in some, it was even higher than normal. Secondly, there were no significant differences in the haemoglobin values between patients with normal and elevated serum erythropoietin levels. Comparison between average serum erythropoietin levels in patients

Table 3. Values of serum erythropoietin in patients with different severity of anemia (n=50).

Haemoglobin (g/l)	Number of patients	Serum erythropoietin (U/l)
72-100	10	15.9±11.9
101-110	13	12.3±8.8
111-120	16	18.1±10.5
Above 120	11	12.5±9.3

Table 4. Values of serum erythropoietin and hemoglobin in untreated patients and patients treated with different doses of recombinant erythropoietin (n=50).

Dose of recombinant erythropoietin (UI/седм.)	Number of patients	Haemoglobin (g/l)	Serum erythropoietin (U/l)
0	13	101.9±23.1	8.5±5.9
500-2000	13	114.3±10.4	13.9±10.1
3000-4000	16	116.2±7.2	18.6±11.3
6000-9000	8	105.4±11.4	19.7±8.8

Table 5. Values of haemoglobin and serum erythropoietin, and dose of recombinant erythropoietin in groups with different stage of CRF (n=50).

Serum creatinine (mcmol/l)	Number of patients	Haemoglobin (g/l)	Serum erythropoietin (U/l)	Dose of recombinant erythropoietin (UI/ седм.)
Below 150	11	114.9±17.9	16.4±12.6	3417±2200
151-225	13	108.5±12.8	12.4±7.8	3150±1203
226-300	13	109.8±15.7	16.2±11,4	3444±1667
301-600	13	108.5±15.3	15.0±9.5	3000±2654

with different severity of anaemia also showed a lack of significant relation with haemoglobin values. An elevation of serum erythropoietin level after increasing the dose of recombinant erythropoietin, used to treat renal anaemia, was found. Only the difference between the values of serum erythropoietin in untreated with recombinant erythropoietin and treated with the highest dose was significant. Overall, there was no relation between the serum erythropoietin level, the severity of anaemia and the severity of CKD.

Discussion

Although data for the advantages of treatment of RA in CRF are enough, the question at which stage of renal dysfunction erythropoietin treatment should begin to reduce complications remains a topic for discussion. One of the reasons for this is the lack of measuring parameters of erythropoietin synthesis [7].

Publications for measurement of the level of serum erythropoietin in patients with CRF are very few. The review shows that most of them have been published in the period 1977-2000 year. Many of these publications [8-11] summarise the results of studies with a very small number of people.

M. Chandra et al. [8] researched 48 children with CRF. They found a significant correlation between haemoglobin and creatinine clearance but did not analyse erythropoietin levels in different stages of CRF.

Y. Fukushima et al. [9] tested the serum level of erythropoietin in 13 predialysis patients. They discovered that it was increased in all the patients with severe anaemia at the same time. The authors interpret this association as a result of the highly increased levels of inhibitors of erythropoietin.

McGonigle et al. [12] found out in a test of 60 patients with different stages of CRF that the average level of erythropoietin was slightly elevated, and there was no connection with the serum creatinine value. They also found an exponential increase in serum erythropoietin when haematocrit dropped below 32%.

P. Garimella et al. [13] summarised the Health, Aging and Body Composition Study results and revealed no interaction between serum erythropoietin with chronic kidney disease and anaemia.

M. Rahman et al. [14] studied 60 patients with different stages of CRF. They found very low levels of serum erythropoietin (2,67±2,36 mUI/ml) and a lack of significant connection with creatinine and serum iron and ferritin.

In a study by W. Korte et al. [10], which included 17 patients, significant damage to the regulation of erythropoietin in slight renal dysfunction was noticed. The authors concluded that patients with mild renal dysfunction and unexplained anaemia should be investigated for erythropoietin concentration and that substitution therapy should be considered when the erythropoietin concentration is found inadequate for the degree of anaemia.

Data from these six publications [8-10, 12-14] did not allow us to compare with the data from our investigation.

Radtke et al. [15] studied the erythropoietin level in 135 patients with creatinine clearance from 2 to 90 ml/min. They found elevated erythropoietin levels in all five groups. In patients with creatinine clearance below 40 ml/min, they discovered non-correspondingly high levels of serum erythropoietin. Our results are different than the cited ones – levels of serum erythropoietin were elevated only in 14/50 of our patients, and the average value of the serum creatinine in them did not differ from the values

of the patients with normal levels of serum erythropoietin.

Pop et al. [11] studied 19 patients with nondialysis CRF. They discovered that the patients treated with erythropoiesis-stimulating agents had twice as high serum erythropoietin levels as the patients who had not been treated with erythropoiesis-stimulating agents. This publication is the only one with a similar comparison; the results fully match ours.

Panjeta et al. [16] studied 356 patients in all stages of CKD. They reported that in patients with CKD-2 and CKD-3, the median values of serum erythropoietin were significantly higher, and in the patients with CKD-4 and CKD-5 – significantly lower compared to healthy people. These authors neither comment on these results nor did they compare them to other publications. Our results are significantly different from those in the cited publication. We found no significant differences between the average values of serum erythropoietin in patients with different severity of renal failure.

In one study of 395 patients [7] randomised from a group of 5000 people, who underwent coronary angiography, it has been confirmed that haemoglobin is significantly lower in patients with GFR below 20 ml/min than in healthy people. Among them, erythropoietin levels are identical, an inadequate indicator for erythropoietin regulation. The authors discovered dependence between serum erythropoietin and haemoglobin only in GFR levels above 40 ml/min and that in lower levels of glomerular filtration, serum levels of erythropoietin remain non-correspondingly high. Our results partially match the results of T. Fehr et al. [7].

The results of our study and the results of some cited authors show that patients with CRF may have normal or low levels of erythropoietin, which do not t correspond to the severity of anaemia, which raises the question of the relative erythropoietin deficiency. The study of T. Fehr et al. [7] is one of the few which tried to find quantitive dependence between erythropoietin levels and haemoglobin in different stages of CRF. According to these authors [7], interpreting serum erythropoietin levels in the context of renal failure remains debatable.

Conclusion

Serum erythropoietin is not tested in the routine practice of renal anaemia treatment in CKD with recombinant erythropoietin, both at the beginning and during treatment, which usually continues for many months and years. Our study is the first one in Bulgaria in which serum erythropoietin level is measured in patients with CKD in a predialysis stage. The results show that, in contradiction to the known rule, only in 6% of the studied patients, the serum erythropoietin level was below the standard value. The average serum erythropoietin level was lower in females, but this is normal in all patients with both genders. In 28% of the patients, the serum erythropoietin level is above the standard value. A difference in the average haemoglobin values was found in patients with different serum erythropoietin values. There are versatile differences in the values of serum erythropoietin in patients with different haemoglobin values and different stages of renal failure. There were differences in the values of serum erythropoietin in patients that had been treated and untreated with recombinant erythropoietin.

The results from this study definitely show that the studies of serum erythropoietin in patients with renal failure should continue and expand.

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