Effectiveness of Treating the Renal Anemia in Chronic Hemodialyzed Patients by Epoietin Alpha and Beta

Edin Ostrvica1, Enisa Mesic2, Dzenana Ostrvica2, Jasmin Delic2, Sunita Delic-Custendil3, Fatima Hukić4
1Health Centre „Dr Mustafa Sehovic” of Tuzla, Bosnia and Herzegovina
2Department of Dialysis, Clinical University Centre of Tuzla, Bosnia and Herzegovina
3Department of Pediatrics, Clinical University Centre of Tuzla, Bosnia and Herzegovina
4Department of Anatomy, School of Medicine, University of Tuzla, Bosnia and Herzegovina
5Polyclinic of Transfusiology, Clinical University Centre of Tuzla, Bosnia and Herzegovina
6Department of Biochemistry, Clinical University Centre of Tuzla, Bosnia and Herzegovina

1. INTRODUCTION
Anemia is an early sign of chronic kidney dysfunction, caused by many different factors, but the insufficient erythropoietin synthesis is the crucial factor in its development. Anemia is defined as a hemoglobin level below 5% out of that in total population (1). Frequency and seriousness of anemia are increased with progression of kidney disease. Renal anemia is found to be more frequent two to three times in patients with diabetes mellitus in comparison to general population at all levels of glomerular filtration (2). Erythropoietin is hematopoietic factor of growth that regulates erythropoiesis stimulating proliferation and differentiation of immature red blood cells. Erythropoietin is secreted by the cells of peritubular interstitial of the kidney cortex. A small amount of erythropoietin is synthesized in the liver, lungs, spleen, capillary endothelium and sex glands (3). Depending on percentage of carbohydrate component participation (erythropoietin is glycoprotein) in a molecule, we distinguish two forms of erythropoietin: Erythropoietin alpha and beta. Diagnosis of renal anemia is made in the case of renal dysfunction, and in the case when in the course of estimation none of other possible causes of anemia was found. Diagnostic procedure in chronic renal patients should be performed in all cases if the level of hemoglobin is below 11,5 g/dL in adult women, 13,5 g/dL in adult men and 12 g/dL in men older than 70 years. European register for improvement the practice (European Best Practice Guidelines-EBPG) suggests for all the chronic renal patients maintaining target hemoglobin above 11 g/dL, and hematocrit above 33% (4). Introducion of recombinanat human erythropoietin (rHuEPO), in the course of 80-ieth years of the last century revolutionary progress was made in the renal anemia treatment. So, presently most of renal patients are not anemic and live more qualitatively than before (5). EBPG recommends administration of rHuEPO to all the patients suffering from chronic renal disease, hemoglobin level below 11 g/dL (hematocrit lower than 33%), measured two times in the course of two weeks, if all the other causes of anemia are excluded. The application procedure of rHuEPO is intravenous, subcutaneous, and intraperitoneal, depending on the patients’ group and the type applied. Comparison of subcutaneous and intravenous application of epoietin revealed stronger reticuloocytes respond (reaction) after subcutaneous application of either epoietin alpha or epoietin beta (6).

2. OBJECTIVES
The objective of our study was to compare effectiveness of epoietin alpha and beta application in the treatment of renal anemia treatment of hemodialysis patients.

3. PATIENTS AND METHODS
Prospective randomized study was performed in the Department Of Nephrology, Dialysis and Kidney Transplantation, Clinic of Internal Diseases, UKC Tuzla, in the course of six months. The group included 60 patients, both sexes, randomly chosen, average age 55.3 ±13.38 (27-80 years old). Criteria for including patients into the study were: older than 18 years, haemodialyzed longer than three months and treated by epoietin beta, stable level of hemoglobin, between 9 and 11 g/dL at least two successive measurements.

ORIGINAL PAPER SUMMARY
Introduction: Anemia is an early sign of chronic kidney dysfunction, caused by many different factors, but the insufficient erythropoietin synthesis is the crucial factor in its development. Objectives: The objective of our study was to compare effectiveness of epoietin alpha and beta application in the treatment of renal anemia in chronic hemodialyzed patients. Patients and methods: The group included 60 patients of both sexes, randomly chosen. Criteria for including patients into the study were: older than 18 years, haemodialyzed longer than three months and treated by epoietin beta, stable level of hemoglobin, between 9 and 11 g/dL at least two successive measurements and no malignant disease present. The patients were then randomized into groups: 20 patients were administered epoietin alpha intravenously instead of epoietin beta subcutaneously (experimental group); 20 patients were administered intravenously epoietin beta instead of epoietin beta subcutaneously (control group A), the rest of 20 patients were administered epoietin beta subcutaneously (control group B). All the testees were administered epoietin alpha or beta three times weekly after haemodialysis, intravenously or subcutaneously. Results: Comparison among mean values of hematological and biochemical parameters before starting the treatment by erythropoietin, and third and sixth months after therapy in the studied groups, no significant difference was found (p>0.05). Conclusion: Epoietin alpha and beta showed approximate degree of efficacy in renal anemia treatment of hemodialysis patients. The way of erythropoietin administration did not significantly affect the level of hemoglobin and hematocrit in six months research period.

Keywords: epoietin, renal anemia, chronic hemodialyzed patients
and no malignant disease present. Before inclusion into examination blood picture was analyzed (erythrocytes, leukocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, and thrombocytes), TIBC, UIBC, ferritin, electrolytes, CRP, proteinogram, transaminases and Kt/V (measure of dose for dialysis). The patients were then randomized into groups: 20 patients were subcutaneously (control group, subgroup A), the rest of 20 patients were intravenously instead of epoietin beta subcutaneously (experimental group); 20 patients were included into examination blood picture was analyzed (erythrocytes, leukocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, and thrombocytes), TIBC, UIBC, ferritin, electrolytes, CRP, proteinogram, transaminases and Kt/V (measure of dose for dialysis). The patients were then randomized into groups: 20 patients were subcutaneously (control group, subgroup B). The rest of 20 patients were administered epoietin alpha intravenously (table 2).

4. RESULTS

Comparison of mean values of parameters of the blood picture (erythrocytes, leukocytes, hemoglobin, hematocrit, and thrombocytes), iron, ferritin, TIBC, UIBC, TBF, CRP, and control groups) a month before admission of erythropoietin and after three-month therapy, no significant difference was found (p>0.05). After six month-application of epoietin (alpha and beta) in renal anemia treatment, significant difference only in erythrocytes number was found (p=0.02) (table 4). Differences in frequency in achieving target values of hemoglobin (<11 g/dL) and hematocrits (>33%) at the start of therapy were registered, in relation to the achieved target values before and after the therapy. For all the calculations we used the significance level of p≤0.05.

5. DISCUSSION

Correction of anemia is one of the most important tasks in renal patients’ care, regardless to preterminal or terminal phase of chronic renal disease (7). Some studies show that higher level of hemoglobin is in relation to the mortality risk and hospitalization (8), and most of life quality indicators were improved in patients with higher concentration of hemoglobin. In our study most testees have hemoglobin level between 10 and 11 g/dL, and hematocrit between 32 and 34%, after six month-therapy. The best results in the treatment...
were achieved in the patients on subcutaneous epoetin beta therapy. Namely, this group of patients after six-month therapy achieved hemoglobin values above 11 g/dL and hematocrit above 33%, what is in accordance to EBPG recommendations. After six-month therapy erythrocyte number was also significantly different in comparison to the other two groups (p=0.002). Somewhat poorer effects of the treatment were achieved in the patients treated by epoetin alpha (average hemoglobin 10.3 g/dL and hematocrit 32%), with no significant difference. The patients on intravenous epoetin beta therapy had average hematocrit 33%, and the lowest average hemoglobin of 9.9 g/dL in comparison to the other groups of patients. Such a relation between hemoglobin and hematocrit is not in accordance to the findings in the study where hemoglobin concentration in the peripheral blood reflects total mass of erythrocytes (9). It has to be mentioned that comparison of the erythrocyte and hematocrit number before starting with subcutaneous therapy by epoetin beta, and after six-month therapy, no statistically significant difference was found. However, as the erythrocyte and hematocrit number were increasing in the course of the last three months, the difference tended to statistical significance (p=0.08 and p=0.07), we could suppose that prolonged therapy under the same conditions could lead soon to statistically significant difference in these parameters. Predialysis concentration of hemoglobin abore 14 g/dL in this study was found in none of the patients, so danger of hemoconcentration in the course of haemodialysis was not present (10). Comparison of thrombocyte number values in the course of six-month therapy by epoetin alpha and beta did not show significant difference (p=0.05). Though there are studies that show agents stimulating erythropoiesis improve thrombocyte function (11), in our patients thrombocyte values were in the limits of referential values. Thromboembolism development in the experimental period was noted in none of patients. Explanations for the results obtained could be found in dialysis by means of native fistula, as we had not patients with artero-vein graft in our research. Elevation of circulating level of reactants in acute phase of inflammation of one or more cytokinins indicates the presence of inflammation. However, as determination of certain cytokinins is expensive, and serum concentrations of some cytokinins do not always indicate their activity in tissues, their application has not been recommended yet in routine clinical practice (12). That is why we in our research took CRP as the main indicator of acute inflammatory process, and as an additional indicator we took leucocytes number. Though all our testees are chronic renal patients and CRP is most known indicator of acute phase of inflammation, it was important to control CRP because its high level and inflammation is often associated with anemia, and with increased needs for erythropoietin, as well. Our research results show no significant differences in CRP values among the tested groups (p=0.05). It should be mentioned that average values of CRP were on upper limits of referential values, or moderately increased, measured after six-month therapy in all the groups of patients. High level of CRP is probably an outcome of some systemic factors connected to uremia or some factor depending on hemodialysis. In our study significant differences were not present either in leucocyte number among researched groups (p=0.05). Average leucocyte number was out of limits of referential values in no group of patients. However, it is interesting that our results do not show correlation between CRP and leucocytes in no group of patients. Namely, the highest average values in leukocytes number were followed in average by the lowest level of CRP. When the leucocytes number was lower, CRP values were higher. Possible cause for that are abnormalities of immune system in hemodialysis patients partly developed as a result of uremia, and partly as a direct result of the therapy.

6. CONCLUSION

Epoetin alpha and beta showed approximate degree of efficacy in renal anemia treatment of hemodialysis patients. To achieve and maintain target values of hemoglobin and hematocrit in such patients, approximately equal doses of epoetin alpha and beta were needed. The way of erythropoietin administration (intravenous or subcutaneous) did not significantly effect the level of hemoglobin and hematocrit in six months' research period.

**REFERENCES**


**TABLE 3.** Basic statistical characteristics for the parameters analyzed for the group of patients treated by epoetin beta subcutaneously (control group, subgroup B)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>30 days before therapy</th>
<th>After 90 days of therapy</th>
<th>After 180 days of therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes (x1012/L)</td>
<td>3.2 ± 0.27</td>
<td>3.2 ± 0.39</td>
<td>3.4 ± 0.31</td>
<td>0.08</td>
</tr>
<tr>
<td>Leucocytes (x109/L)</td>
<td>5.3 ± 1.48</td>
<td>5.5 ± 1.75</td>
<td>5.4 ± 1.62</td>
<td>0.86</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.2 ± 1.70</td>
<td>10.1 ± 1.84</td>
<td>10.1 ± 2.03</td>
<td>0.18</td>
</tr>
<tr>
<td>Hematocrit (L/L)</td>
<td>0.32 ± 0.03</td>
<td>0.32 ± 0.03</td>
<td>0.34 ± 0.03</td>
<td>0.07</td>
</tr>
<tr>
<td>Thrombocytes (x109/L)</td>
<td>171.9 ± 51.84</td>
<td>173.6 ± 47.07</td>
<td>173.0 ± 52.42</td>
<td>0.99</td>
</tr>
<tr>
<td>Iron (µmol/L)</td>
<td>15.3 ± 8.56</td>
<td>15.2 ± 8.95</td>
<td>15.3 ± 10.23</td>
<td>0.79</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>4065.3 ± 480.67</td>
<td>775.6 ± 612.42</td>
<td>743.4 ± 482.52</td>
<td>0.22</td>
</tr>
<tr>
<td>UIBC (µmol/L)</td>
<td>24.6 ± 6.64</td>
<td>24.7 ± 12.93</td>
<td>19.7 ± 10.02</td>
<td>0.39</td>
</tr>
<tr>
<td>TIBC (µmol/L)</td>
<td>38.2 ± 1.92</td>
<td>38.4 ± 10.32</td>
<td>37.4 ± 8.93</td>
<td>0.96</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5.1 ± 8.02</td>
<td>6.9 ± 12.94</td>
<td>3.7 ± 4.36</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Corresponding author:** Edin Ostvrca, MD, Health Centre “Dr Mustafa Sehovic”, Tuzla. Albina Herijevica 1, Bih, Tel. 06646930, e-mail: edinostvrca@yahoo.com