The Influence of Inflammatory Markers and CRP Predictive Value in Relation to the Target Hemoglobin Level in Patients on Chronic Hemodialysis

Adnan Musanovic1, Senaid Trnacevic2, Mevludin Mekic3, Affan Musanovic4
Clinic of Urgent Medicine, Clinical Center of Sarajevo University, Bosnia and Herzegovina1
Clinic of Nephrology, University Clinical Center Tuzla, Bosnia and Herzegovina2
Department of Heart Diseases and Rheumatism, Clinical Center of Sarajevo University, Bosnia and Herzegovina3
Department of Radiology, Cantonal Hospital Zenica, Bosnia and Herzegovina4

The aim of this study was to determine the influence of inflammatory markers, predictive values of CRP and target hemoglobin (Hb) in patients on chronic hemodialysis. Material and methods: Made is a cross-sectional study of inflammatory agents serum levels—CRP, fibrinogen and ferritin before hemodialysis in 114 patients divided into two groups according to the achieved or unachieved target hemoglobin level in the Cantonal Hospital in Zenica. Results: The 57 patients (test group) did not reach the target hemoglobin in the range from 10-12 g/dl and CRP values were significantly higher compared to the control group (57 patients) who had reached targeted hemoglobin values. Levels of fibrinogen and ferritin were not significantly different between the control and the test group. CRP values are in negative correlation with the Hb concentration, while fibrinogen and ferritin values had a positive correlation. Significant negative correlation was only found in case of CRP, respectively, higher CRP was at lower levels of blood Hb. It was found that the predictive value of CRP is 6.5 mg/L to achieve target Hb level. If the CRP increases by 1 mg/L, possibilities to achieve the target Hb level in dialysis patients is reduced by 7.5%, with a sensitivity of 51% and specificity of 77%. Ferritin was elevated due to iatrogenic iron saturation, because all patients received intravenous iron and was treated with erythropoietin. By identification and analysis of inflammatory agents and duration of hemodialysis, are explored the primary influence on hematopoiesis, of course, with the primary application of erythropoietin and adjuvant agents. It has been shown that CRP alone has an impact on the target Hb level, depending on the hemodialysis duration. Conclusion: The research results show how what looks as routine findings may be helpful in the timely detection of threatening complications and their treatment, and provide extended and improved quality of life for patients on hemodialysis. Key words: Inflammatory markers, CRP, target hemoglobin, hemodialysis

1. INTRODUCTION

Anemic syndrome can occur as a primary disease, the result of another disease or as a complication. It is believed that the occurrence of anemia depends on the age, gender, ethnicity, altitude. If you live in the lower elevations below 1500 meters anemia is a condition where Hb level is lower than 11.5 g/dL for adult women and lower than 13.5 g/dL for men, and less than 12 g/dL for men over 70 years of age (1, 2). According to the World Health Organization definition of anemia are hemoglobin level below 12 g/dl in men and less than 13 g/dl in women.

Often dialysis is initiated in patients who have a significantly lower Hb than normal and it is considered that even then there are many problems in the organs due to anemia, which are direct factor of mortality. It is believed that the anemia occurs, or it is noticed, or considered when the symptoms and signs are visible and pronounced. In diabetes mellitus, anemia develops earlier and is in more severe form when the GFR is 45 ml/min, three times more common than at the same GFR due to other reasons chronic renal insufficiency or transient renal insufficiency (3). The reason for this phenomenon is the renal hyperfiltration, changes in the magnesium level, serum osmolality and deformed red blood cells. Therefore, the mere presence of anemia requires treatment and it is not comparable with the degree of GFR decrease.

To the occurrence and degree of anemia also contributes the loss of folates, especially in patients on hemodialysis (3, 4) because they have less iron...
reserves. A special effect has age among hemodialysis patients, because Hb decreases with age and 50% of hemodialysis patients are older than 60 years (5).

In hemodialysis patients, because of apparent impaired renal function, the most likely reason is the lack of erythropoietin (2) or agents that stimulate erythropoiesis (ESA).

2. MATERIAL AND METHODS

A cross-sectional study was performed in which were tested the serum inflammatory parameters and hemoglobin concentration in the dialysis population. The study included 114 chronic patients on hemodialysis at the Cantonal Hospital Zenica, Department for Hemodialysis within Service for Internal diseases since 2010, who are dialyzable three times a week for 4 hours, according to the regular protocol of hemodialysis at the Cantonal Hospital Zenica at the Department for hemodialysis. Hemodialysis is performed on appliances FreseniusMC 4008, Fresenius 5008, Braun Dialog. All patients had a diagnosis of end-stage renal disease on the basis of official criteria and diagnostic parameters which are recorded in their medical records and records or dialysis plan in their dialysis notebooks. Monitoring of dialysis patients is performed, beside periodic laboratory tests also by other examinations of nephrologist according to official recommendations and guides for hemodialysis (6).

Inclusion criteria were chronic patients on hemodialysis who were according to the targeted Hb level divided into two groups. The first group (test group) included chronic patients on hemodialysis who in time of study did not achieve target Hb level in the range from 10-12 g/dl, and the second group (control) those who did not reach the target Hb level below 12 g/dl. Within these groups are analyzed data on CRP, fibrinogen and ferritin taken before hemodialysis. Hemoglobin is correlated with parameters of inflammatory response.

The statistical methods used are: mean, standard deviation and median with interquartile range, depending on the distribution of data, symmetrical or asymmetrical, while the frequencies were presented by the absolute and relative numbers. For comparison of continuous variables Student’s t test for independent samples was used or Mann-Whitney U test. The univariate analysis of variance and Kruskal-Wallis test tested the difference between the three groups of patients. Pearson and Spearman correlations were used for correlation analysis and for the analysis of categorical variables the chi-square test. To predict the outcome of the targeted Hb level was used univariate logistic regression and to determine the „cut off” for the target Hb ROC curve analysis.

3. RESULTS

The study included 114 patients at mean age of 55 (45-67 years), 56 men (49%). Analysis of the patient age indicate that the mean age in the test group was 54 years (range 44-65 yrs.) and 55 (range 47-67 yrs.). Also if we look at the male:female ratio we can notice that it was 27:30 in the Test and 29:28 in the Control group without significant differences in relation to age and gender between control and test groups of patients. In the test group, the average values of CRP were significantly elevated (mean 6.5, range 3.2-15.8) compared to the average values in the control group (mean 3.2, range 3.2-6.3). Average values of fibrinogen and ferritin in the test (mean 3.5±1.2) and control (mean 3.5±1.2) groups were not significantly altered.

All patients on hemodialysis were treated with iron preparations, which is a prerequisite and an essential parameter for monitoring of anemia syndrome in these patients. In clinical practice it is administered intravenously by preparation known as Venofer. Iron values are interpreted by ferritin values which were slightly higher in the test group (mean 700, range 328-1534) compared with the control group (mean 632, range 277-988). There was no significant difference between serum ferritin level in test and control group compared to Venofer administration. If we compare the average value of ferritin in all groups that had administered Venofer or not we obtained significant differences in the concentration (Figure 1).

There is no significant correlation in the test (rho=−0.13) and control group (rho=−0.18) in between hemoglobin concentration and average CRP values. The sample is very small so such a correlation is positive and there is no difference in the test and control group. In all studies in the control and test group was examined the correlation between individual parameters within these groups and not the difference compared to the control and test groups.

If we analyze the result of the correlation between CRP and hemoglobin in the entire group of 114 patients we found a significant correlation (rho=−0.2). This means that if the patient has higher concentrations of CRP the hemoglobin levels will be lower.

There was no significant correlation in the test (rho=0.17) and control group (rho=0.01) between the concentration of fibrinogen and hemoglobin.

The correlation coefficient is positive between concentration of fibrinogen and hemoglobin with r = 0.1 and which is not statistically significant.

There is no significant correlation between serum ferritin concentration and hemoglobin in the test (rho=−0.19) and control group (rho=−0.12). The sample is very small and there is no difference between the test and control groups between ferritin and hemo-

![Figure 1. Ferritin values in relation to Venofer administration](image)
The Influence of Inflammatory Markers and CRP Predictive Value in Relation to the Target Hemoglobin Level in Patients on Chronic Hemodialysis

...duration in the test and control group.

Table 3. Trend of Hb values by groups according to dialysis duration in the test and control group

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unit of change</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>mg/L</td>
<td>1.07</td>
<td>1.0 – 1.14</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 4. The association between CRP and the target Hb level in baseline sample. Legend: OR-odds ratio, CI-confidence interval, p-significance level

The essence is that the inflammatory processes in particular interleukins are blocking macrophages and iron is „trapped” in these cells. It was found that the migration of leukocytes in these patients is reduced or damaged and slowed, which is reflected in the use of ferritin concentration and the efficiency of erythropoiesis (7, 8, 9).

If these parameters are analyzed and presented statistically in all 114 patients there was a significant association between ferritin, CRP, the group that received EPO and the target Hb level. In the analysis of fibrinogen and the target Hb in all patients there was no significant correlation or impact on the value of the target Hb. However, CRP and ferritin were asymmetrically distributed. After their logarithmic transformation it is shown their clear correlation with the value of Hb, (p<0.05), indicating a connection between inflammation and anemia, regardless of the median CRP which is within normal values and regardless of iron supplements.

Figure 2. ROC analysis of the relationship between CRP and the target Hb level.

The essence is that the inflammatory processes in particular interleukins are blocking macrophages and iron is „trapped” in these cells. It was found that the migration of leukocytes in these patients is reduced or damaged and slowed, which is reflected in the use of ferritin concentration and the efficiency of erythropoiesis (7, 8, 9).

If these parameters are analyzed and presented statistically in all 114 patients there was a significant association between ferritin, CRP, the group that received EPO and the target Hb level. In the analysis of fibrinogen and the target Hb in all patients there was no significant correlation or impact on the value of the target Hb. However, CRP and ferritin were asymmetrically distributed. After their logarithmic transformation it is shown their clear correlation with the value of Hb, (p<0.05), indicating a connection between inflammation and anemia, regardless of the median CRP which is within normal values and regardless of iron supplements.

Treatment of renal anemia with erythropoiesis-stimulating agent (ESA), which is called erythropoietin is a practice which proved to be effective in eliminating the symptoms and reduce complications of anemia. Analysis of three European studies for efficiency of treatment of anemia in patients with CKD, showed that most patients do not begin receiving erythropoietin until they reach stage 5 CKD, or until they reach dialysis (10, 11, 12). There is strong evidence from randomized trials in CKD patients on dialysis that erythropoietin, called s.c. epoetin, is equally effective as i.v. epoetin and may be used at lower doses and therefore reduce the
cost of treatment. Dose required for s.c. epoetin (alpha or beta) are by 22% less than those for i.v. epoetin (13, 14).

Central place in the study of inflammatory parameters in hemodialysis belongs to CRP because of its importance as an inflammatory marker due to its sensitivity and reliability and repeatability with the very early appearance in serum of significantly increased concentration within inflammatory processes (14,15,16,17).

Elevated levels of CRP induced a decrease of Hb levels, or anemia occurrence with p<0.05 as statistically significant. Higher CRP levels exist when there is a lower Hb level. From the mechanisms of creation and loss of RBC and Hb as well as the appearance of markers of inflammation, it is considered that the development of anemia, besides wear also has loss and toxic effects of basic inflammatory and immunological processes before hemodialysis, while after hemodialysis Hb loss is minimal. In our patients were still active primary processes that led to uremia. Analysis of the results of the CRP according to Hb values is essential because the CRP is relevant factor in inflammation. Central part of research is the relationship of inflammatory agent CRP as a synonym of inflammation and Hb. The relationship of these parameters was analyzed by logistic regression analysis. In our research, the value of CRP of 6.5 mg/L is only an indication that the concentration is higher by almost 50% of normal but is still in clinical practice relatively "low" compared to the values that we obtain in the process of uncomplicated, general, viral or bacterial infections. We noticed that this value during follow-ups as a rule is lowest increased value and following are usually with higher value. With a resolution of disease the decrease of CRP is very fast. Reduction in CRP level by 1 mg/L increased the chance of reaching the target Hb. It is quite understandable for the group with Hb<10, but unexpectedly for the group with Hb>12, because here existed a positive correlation, or the higher CRP corresponds to higher Hb and vice versa. This may be the greatest value of this study, because it is unexpected, that may be proposed for further research in this field and serve as an explanation for why normal blood count is a risk factor for mortality in uremia.

ROC analysis represents an analysis of the relationship between CRP and the target Hb with a certain level of prediction. Average CRP of 6.5 mg/L with a sensitivity of 51% and specificity of 77% discriminating between achieved and not achieved target Hb level, with AUC = 0.61 (p = 0.03). That means, if the CRP values are less than 6.5 mg/L, the patient will achieve the target Hb with reliability of 51% and specificity of 77%, while if CRP is above 6.5 mg/L it means that the target Hb level is not achieved, so we should look for the reasons for increased CRP. CRP level of 6.5 mg/L is shown as a „cut off point” with a sensitivity of 51% and specificity of 77% in discriminating between achieved and not achieved target Hb, with AUC = 0.61 (p=0.03) is a perfect orientation in clinical practice. There is a positive correlation between fibrinogen and Hb, which indicates that fibrinogen has no influence on the occurrence of anemia, p>0.05 which statistically is not significant.

Fibrinogen is one of the most significant factors of inflammation and it is associated with a significant percentage of survival in hemodialysis patients. Fibrinogen is, in addition of role as inflammatory marker, significant in numerous processes of coagulation and thrombosis.

In inflammatory and other processes ferritin is blocked in macrophages and his release and use is not possible (7). As a rule are also determined values of proteins carriers of serum iron.

It is believed that if the ferritin level is above 800 ng/ml, iron should not be administered in order to achieve the target Hb (18,19). However, the mobilization of iron from the depot is not an easy process, and sometimes the release and use of iron is not accompanied with the same concentration in the serum. Unknown are influences of other metals on the mechanism of iron use. Probably enzyme disorders are in the basis of these disorders (20,21).

Ferritin was significantly highest in the group that was on dialysis up to 10 years, which in turn is associated with iron supplements.

5. CONCLUSIONS

There is a connection between anemia and inflammation in the conducted research. The duration of dialysis was not associated with anemia due to rational therapeutic approach, especially adequate administration of erythropoetin and iron preparations.

REFERENCES