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THE INFLUENCE OF ACE INHIBITORS TREATMENT ON ANEMIA PARAMETERS IN PATIENTS ON MAINTENANCE HEMODIALYSIS

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Angiotensin-converting enzyme inhibitors (ACEI) are commonly prescribed to chronic kidney disease (CKD) patients due to their beneficial effect on the cardiovascular system. It is not completely understood whether ACEI treatment has an influence on anemia parameters in hemodialysed (HD) patients.

The aim of this study was to investigate the correlation between use of ACEI and anemia parameters in HD patients receiving erythropoiesis-stimulating agents (ESA).

This cross-sectional study included 114 HD patients divided into two groups: ACEI antihypertensive treatment group and other antihypertensive treatment group (calcium the antagonists, β blockers). According to the equivalent dose of ACEI, patients were subdivided into three subgroups: I subgroup (low dose of ACEI <10mg/day), II subgroup (median dose of ACEI between 10 and 20mg/day) and III subgroup (high dose of ACEI >20mg/day).

ACEI antihypertensive treatment group had statistically lower number of red blood cells (RBC) (3.17±0.39 vs. 3.33±0.29mmol/L, p=0.016), hemoglobin level (98.68±12.06 vs. 104.94±7.77g/dL, p=0.001) and hematocrit (29.35±3.45 vs. 31.19±2.27, p=0.002) compared to the other antihypertensive treatment group. According to ACEI dosage, there were no significant differences between all three subgroups in the values of anemia parameters and mean arterial pressure (MAP). The statistical difference between subgroup I and non-ACEI group was found in MAP value (χ^2=5.143, p=0.023). The statistical differences between subgroup II and non-ACEI group were found in the number of RBC, hemoglobin levels, hematocrit and MAP (χ^2=4.980, p=0.026; χ^2=8.176, p=0.004; χ^2=9.013, p=0.004; χ^2=4.393, p=0.036, respectively) and between subgroup III and non-ACEI group in hemoglobin level, hematocrit and MAP (χ^2=4.525, p=0.033; χ^2=4.317, p=0.038; χ^2=8.733, p=0.003, respectively).

Our study demonstrates that ACE inhibitors treatment negatively correlates with anemia parameters in HD patients. The determination of an adequate dosage of ACEI to provide satisfactory cardioprotection, but not to jeopardize erythropoiesis, should be a therapeutical goal. *Acta Medica Medianae 2017;56(3):107-115.*

Key words: *angiotensin-converting enzyme inhibitors, anemia, hemodialysis, erythropoietin, hypertension*

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Introduction

The prevalence of anemia escalates with the progression of chronic kidney disease (CKD) predominantly by reason of impaired kidney function to produce erythropoietin and negative effects of the uremic toxins on bone marrow function. The treatment of anemia with erythropoiesis-stimulating agents (ESA) is the mainspring of improving the quality of life (1, 2) and reducing the need for red blood cell transfusions in patients with end stage renal disease (ESRD) (3, 4). However, there is variability in sensitivity to ESA, namely 5-10% of CKD patients show weak responses (3). The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) has defined ESA resistance as being present when patients do not achieve the recommended hemo-globin (Hb) target level (110-120 g/L), despite a treatment with ESAs over several months (5). This hyporesponsiveness to ESA

treatment has been associated with iron deficiency, inflammation, oxidative stress, malnutrition, hyperparathyro-idism, inadequate dialysis, and with numerous other factors (6, 7). ESA resistance increases a risk for stroke, cardiovascular events and mortality rate in CKD patients (8), therefore, it is of para-mount importance to manage this resistance.

The renin-angiotensin system regulates blood pressure controlling vascular resistance and plasma volume. The importance of renin-angiotensin system in erythropoiesis was thoroughly investigated in recent past (9-11). Angiotensin-converting enzyme (ACE) stimulates the mitosis of stem cell and the differentiation of erythroid progenitors (12, 13). Angiotensin II type 1 receptors were found on the surface of erythroid progenitor cells in the bone marrow. Angiotensin II (AT II) acts as a growth factor, stimulating erythroid progenitor cells, and thereby enhances secretion of erythropoietin (EPO). In cooperation, AT II and EPO increase red blood cell mass (11). In the research with healthy volunteers, it was demonstrated that ACE inhibitor (ACEI) treatment decreases the serum AT II level, which consequently results in decline of serum erythropoietin concentration (14). Furthermore, ACEI or AT II receptor blockers (ARBs) have been reported as effective treatment in reactive altitude polycythaemia after renal transplantation (15). Due to positive effect on survival (16), beneficial effect on left ventricular hypertrophy, oxidative stress and endothelial cell dysfunction (17-19), the ACEI antihypertensive treatment is commonly prescribed to CKD patients. It is not completely understood whether or not ACEI treatment has an influence on anemia parameters. The aim of this study was to investigate the correlation between the use of ACE inhibitors and anemia parameters in HD patients receiving ESA.

Patients and methods

The maintenance haemodialysis patients receiving ESA therapy were enrolled from the Clinic of Nephrology, Clinical Center Niš. The study was performed respecting the principles of evidence-based medicine and in accordance with the Declaration of Helsinki. This cross-sectional study included 114 HD patients under ESA therapy and under antihypertensive therapy for at least three months. Patients had been receiving intravenous iron replacement therapy to achieve ferritin level of 300-400 ng/mL and transferin saturation level of 30-40%. Exclusion criteria were: patients undergoing haemodialysis treatment less than three months, patients receiving ESA less than three months, patients taking antihypertensive therapy less than eight months and patients who have changed treatment modality. The patients were divided into two groups: the first group of patients were taking ACEI and the second group of patients were taking other drugs (calcium antagonists, β blockers) in their antihypertensive therapy. Patients were consuming four types of ACEI: fosinopril, ramipril, enalapril and zofenopril. Equivalent dose of ACEI were calculated as stated in Outcomes Based Therapeutic Interchange: An ACE Inhibitor Interchange Program (20) and fosinopril was used as target ACEI. According to the equivalent dose of ACEI, patients were subdivided into three groups: I subgroup (low dose of ACEI <10mg per day), II subgroup (median dose of ACEI between 10 and 20mg per day) and III subgroup (high dose of ACEI >20mg per day). All patients underwent haemodialysis 3 times per week for 4 hours using polysulfone dialyzers, bicarbonate dialysis solution and standard heparinization. Blood samples were taken before the initiation of dialysis sessions.

Hematological and routine biochemical analysis, hemoglobin level (HGB), hematocrit (HCT), number of erythrocyte (RBC), leukocyte (WBC) and platelets (PLT), serum iron (Fe), total iron binding capacity (TIBC), unbuffered iron binding capacity (UIBC), transferin saturation, serum level of albumin (ALB), total proteins (TP), glucose (GLU), cholesterol (CHOL), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), urea (URE), creatinine (CRE) and the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) were measured by standard methods in Biochemical laboratory at the Clinic of Nephrology. Hematological parameters were analyzed on hematology analyzer Nihon Kohden (Japan), while biochemical assessments were performed on the Automatic biochemistry analyzer Erba XL-600 (Erba diagnostics Mannheim, GmbH, Germany). C-reactive protein serum levels were determined using immunoturbidimetric method, on Olympus AU-600 automated analyzer (Olympus Diagnostic, GmbH, Germany).

Blood pressure was measured before dialyses session. Mean arterial pressure was calculated according to the formula: MAP = (2×SBP + DBP)/3, where: SBP- systolic blood pressure, DBP-diastolic blood pressure.

The measurement of dialysis adequacy was evaluated by Kt/V index, calculated according to the Daugirdas formula: Kt/Vsp=-ln(C2/C1-0008xT)+(4-3.5xC2/C1)xUF/W, where: C1-the predialysis urea value (mmol/L), C2-postdialysis urea value (mmol/L), T-hemodialysis duration (h), UF-interdialysis yield (L), W-body weight after hemodialysis session (kg).

ESA therapy included epoetin alpha, epoetin beta and darbepoetin alpha. The dosage of darbepoetin alpha in microgram was multiplied by 200 to obtain the equivalent dose in international units (IU) of erythropoietin (21). We calculated ESA Resistence Index (ERI), defined as the weekly weight-adjusted ESA dose (U/kg/week) divided by hemoglobin level (g/dL).

Statistical analysis was performed using the statistical package SPSS software version 20.0 (SPSS Chicago, IL, USA). A value for $p < 0.05$ was

considered statistically significant. Clinical and biochemical data were compared using the t-test for normally distributed data (expressed as mean±SD) and Mann-Whitney U test for data that were not normally distributed (expressed as Median and IQR in brackets). Correlation analysis was performed using the Pearson correlation test for normally distributed data and Spearman test for not normally distributed data. Kruskal-Wallis test for not normally distributed data was used for the comparison of three and more groups.

Results

Demographic and clinical characteristics of HD patients receiving ESA treatment are presented in Table 1. Baseline characteristics of HD patients did not show statistically significant difference between the two groups. A lower value of Kt/V index was found in the group receiving ACE inhibitors (1.25±0.31 vs. 1.40±0.32, p = 0.011) compared to group receiving other anti-hyper-tensive treatment.

All three values of blood pressure, SBP (137.42±16.30 vs. 125.52±22.85mmHg, p= 0.001), DBP (76.67±6.81 vs. 73.70±7.08 mmHg, p=0.016) and MAP (96.92±9.34 vs. 90.98±10.64 mmHg, p=0.001) were significantly higher in patients on antihypertensive treatment with ACE inhibitors than in patients on antihypertensive treatment with other antihyper-tensive drugs (Table 2).

The HD patients group who were taking ACE inhibitors as antihypertensive drug had statistically lower number of RBC (3.17±0.39 vs. 3.33±0.29 mmol/L, p=0.016), Hb concentration (98.68 ± 12.06 vs. 104.94±7.77g/dL, p=0.001) and hematocrit (29.35±3.45 vs. 31.19±2.27, p= 0.002) compared to HD patients who were taking other antihypertensive drugs. There were no statistically significant differences in iron concentration, TIBC, UIBC and transferrin saturation between the studied groups (Table 3).

Table 1. Clinical and biochemical data of HD patients receiving ACE inhibitors compared to HD patients receiving other antihypertensive drugs

Parameters	HD patients receiving ACE inhibitors as antihypertensive drug (n=60)	HD patients receiving other antihypertensive drugs (n=54)	*t/Z*/c²***	*p*
Age (years)	63.83±10.81 60.00 (57.00-71.75)	62.54±14.59 63.50 (53.75-77.00)	0.534	0.594
Sex (M/F)	38/22	28/26	1.537**	0.215
Duration of HD (months)	53.40±60.72 31.00 (14.00-64.00)	64.22±62.12 44.00 (28.25-77.25)	-1.568*	0.097
Kt/V	1.25±0.31 1.12 (1.08-1.38)	1.40±0.32 1.33 (1.22-1.51)	-2.274	**0.011**
CRP (mg/L)	4.32±3.75 2.90 (1.40-6.00)	5.30±4.97 3.00 (1.52-8.05)	-0.737*	0.461
CRE (μmol/L)	746.71±127.26 730.00 (666.00-831.00)	735.91±169.71 733.00 (624.45-848.00)	0.378	0.706
URE (mmol/L)	25.41± 6.45 24.50 (21.10-29.80)	24.36±5.46 23.50 (20.55-28.40)	0.932	0.353
GLU (mmol/L)	7.11±9.35 5.50 (4.74-6.80)	6.00±2.33 5.34 (4.58-6.72)	-0.477*	0.633
CHOL(mmol/L)	4.73±1.21 4.74 (4.04-5.35)	4.50±1.14 4.44 (3.53-5.45)	1.011	0.314
LDL-C (mmol/L)	2.82±0.95 2.80 (2.20-3.40)	2.65±0.88 2.60 (2.00-3.50)	0.980	0.329
HDL-C (mmol/L)	0.91±0.25 0.84 (0.72-1.10)	0.91±0.25 0.94 (0.75-1.08)	-0.787*	0.431
TG (mmol/L)	2.30±1.46 1.83(1.32-2.86)	2.18±1.84 1.85 (1.27-2.58)	-0.693*	0.489
ALB (g/L)	37.95±2.69 38.00 (36.00-40.00)	37.80±3.18 38.00 (36.75-40.00)	-0.232*	0.817
TP (g/L)	66.90±4.78 67.00 (64.00-69.00)	68.03±4.73 67.45 (65.45-70.92)	-1.261	0.210
ALT (U/L)	19.67±10.52 16.45 (13.40-25.05)	21.51±19.31 17.25 (12.75-22.85)	-0.142*	0.887
AST (U/L)	13.65±5.69 13.25 (9.20-17.62)	16.77±13.70 14.55 (10.00-19.00)	-1.554	0.125
GGT (U/L)	31.55±29.46 21.30 (16.00-30.55)	31.15±26.24 22.00 (13.85-36.40)	-0.043*	0.966

Data are expressed as mean ± standard deviation and median (IQR) or number. *t*-comparison made by Student's t-test, *Z** - comparison made by Mann Whitney U test.

Table 2. Arterial blood pressure in HD patients with ESA treatment

Blood pressure	HD patients receiving ACE inhibitors as antihypertensive drug	HD patients receiving other antihypertensive drugs	*Z*	*p*
SBP (mmHg)	137.42±16.30 140.00 (130.00-150.00)	125.52±22.85 130 (113.75-140.00)	-3.314	**0.001**
DBP(mmHg)	76.67±6.81 80.00(70.00-80.00)	73.70±7.08 75.00 (70.00-80.00)	-2.401	**0.016**
MAP(mmHg)	96.92±9.34 100.00 (90.00-103.33)	90.98±10.64 95.00 (84.58-100.00)	-3.288	**0.001**

Data are expressed as mean ± standard deviation and median (IQR). *Z* - comparison made by Mann Whitney U test.

Table 3. Anemia parameters in HD patients receiving ACE inhibitors compared to HD patients receiving other antihypertensive treatment

Parameters	HD patients receiving ACE inhibitors as antihypertensive drug	HD patients receiving other antihypertensive drugs	*t/Z**	*p*
RBC × 10^{12} (L)	3.17±0.39 3.19 (2.96-3.44)	3.33±0.29 3.31 (3.12-3.51)	-2.443	**0.016**
HGB (g/L)	98.68±12.06 100.00 (89.50-107.00)	104.94±7.77 104.00 (100.75-110.00)	-3.326	**0.001**
HCT(%)	29.35±3.45 29.65(26.82-31.57)	31.19±2.27 31.05(30.17-32.60)	-3.159*	**0.002**
WBC ×10^{9} (L)	7.21±2.04 7.20(5.50-8.60)	6.54±1.81 6.75 (5.10-7.52)	-2.002*	**0.045**
PLT × 10^{9} (L)	189.63±58.55 182.50 (149.25-213.75)	178.06±49.21 169.50 (148.25-205.75)	-0.863*	0.388
Fe (μmol/L)	11.43±5.67 9.35 (7.95-14.45)	11.87±6.47 10.30 (8.50-13.55)	-0.552*	0.581
TIBC (μmol/L)	36.12±5.49 35.80 (32.62-39.47)	35.47±6.86 35.40 (30.65-39.30)	-0.846*	0.398
UIBC (μmol/L)	24.68±6.97 24.84 (21.28-29.03)	23.59±6.56 23.70 (19.13-27.68)	0.856	0.394
Transferin saturation (%)	32.16±15.59 28.48 (21.26-39.60)	33.08±14.19 30.00 (23.80-38.56)	-0.650*	0.516

Data are expressed as mean ± standard deviation and median (IQR) or number. *t*-comparison made by Student's t- test, *Z** - comparison made by Mann Whitney U test.

Table 4. A comparison of clinical variables associated with ERI (erythropoietin resistance index)

Group Variable	ACE inhibitors (n=60)		Other antihypertensive drugs (n=54)	
	r	*p*	*r*	*p*
RBC	-0.445*	**0.000**	-0.466*	**0.000**
HBG	-0.505*	**0.000**	-0.507*	**0.000**
HCT	-0.535*	**0.000**	-0.451*	**0.001**
Fe	-0.190	0.146	-0.334*	0.014
TIBC	0.069	0.599	-0.281*	0.041
UIBC	0.161	0.220	0.066	0.638
Transferin saturation	-0.233	0.073	-0.274*	0.047
CRP	0.139	0.303	-0.035	0.813
Kt/V	-0.010	0.939	0.162	0.244

Data are expressed as Pearson's and Spearman's correlation coefficient (*r*) and *p* value. * Significant correlation

A comparison of clinical variables associated with ERI is presented in Table 4. In patients receiving ACE inhibitors, ERI values were negatively correlated with the number of red blood cells, hemoglobin levels and hematocrit (r=-0.445,p <0.001; r=-0.505, p <0.001; r=-0.535, p <0.001, respectively). Likewise, in patients receiving antihypertensive treatment with other drugs, ERI values were negatively correlated with the number of red blood cells, hemoglobin levels and hematocrit (r=-0.466,p <0.001; r=-0.507, p <0.001; r=-0.334, p=0.014, respectively). In this group of HD patients, iron levels and transferin saturation were correlated negatively with ERI (r=-0.281, p=0.041; r=-0.274, p=0.047, respectively).

Table 5. Characteristics of patients according to ACEI dosage

Group	ACEI (n=60)			Non-ACEI (n=54)	*p value*
Subgroup	I (n=13)	II (n=30)	III(n=17)	IV (n=54)	A,B,C,D,E,F
RBCx10^{12} (L)	3.13±0.51 3.03 (2.79-3.50)	3.12±0.39 3.13 (2.93-3.45)	3.29±0.25 3.28 (3.05-3.28)	3.33±0.29 3.31 (3.12-3.51)	A=0.173 B=0.402 C=0.535 D=0.946 **E=0.026** F=0.188
HBG (gr/L)	94.85±14.86 89.00 (83.50-108.50)	97.70±12.27 99.50 (90.25-104.25)	103.35±7.82 102.00 (98.00-109.50)	104.94±7.77 104.00 (100.75-110.00)	A=0.113 B=0.155 C=0.384 D=0.578 **E=0.004** **F=0.033**
HCT (%)	28.48±4.47 26.80 (25.20-32.15)	29.08±3.44 29.65 (26.50-31.20)	30.48±2.29 26.83 (28.80-32.35)	31.19±2.27 31.05 (30.17-32.60)	A=0.268 B=0.180 C=0.161 D=0.663 **E=0.003** **F=0.038**
Fe (µmol/L)	9.78±3.76 8.80 (6.50-12.80)	13.27±6.88 12.55 (8.27-16.55)	9.48±3.20 8.90 (6.60-11.15)	11.87±6.47 10.30 (8.50-13.55)	A=0.064 B=0.983 C=0.096 D=0.081 E=0.386 F=0.287
TIBC(µmol/L)	34.17±11.39 33.60 (31.95-36.7)	37.00±6.18 36.20 (32.90-40.42)	36.07±5.35 35.30 (32.75-39.45)	35.47±6.86 35.40 (30.65-39.30)	A=0.773 B=0.233 C=0.524 D=0.142 E=0.232 F=0.681
UIBC(µmol/L)	24.39±5.33 24.85 (19.87-28.54)	23.72±7.77 24.82 (21.12-29.00)	26.60±6.52 24.84 (22.47-30.90)	23.59±6.56 23.70 (19.13-27.68)	A=0.388 B=0.426 C=0.122 D=0.771 E=0.522 F=0.705
Transferin saturation(%)	28.94±11.39 26.19 (20.51-40.06)	36.59±18.57 30.69 (26.57-42.16)	26.89±10.01 26.83 (18.90-33.00)	33.08±14.19 30.00 (23.80-38.56)	**A=0.035** B=0.660 C=0.086 D=0.204 E=0.496 F=0.337
MAP (mmHg)	100.27±7.26 100.00 (96.97-101.67)	95.44±10.01 100.00 (86.67-103.33)	96.96±9.36 100.00 (90.00-103.33)	90.98±10.64 95.00 (84.58-100.00)	A=0.545 B=0.700 **C=0.023** D=0.086 **E=0.036** **F=0.003**

Data are expressed as mean ± standard deviation and median (IQR) or number. A (I vs. II), B (I vs. III), C (I vs. IV), D (II vs. III), E (II vs. IV) and F (III vs. IV) represent *p values* of comparison between four groups made by Kruskal Wallis Test

A comparison of clinical variables according to ACEI dosage between the four groups is presented in Table 5. There were no significant differences between all three subgroups (I subgroup ACEI <10mg per day, II subgroup ACEI between 10 and 20mg per day and III subgroup ACEI >20mg per day) in the values of anemia parameters and MAP. The statistical difference between subgroup I and non-ACEI group was found in MAP value (χ^2=5.143, p=0.023). The statistical differences between subgroup II and non-ACEI group were found in the number of red blood cells, hemoglobin levels, hematocrit and MAP (χ^2=4.980, p=0.026; χ^2=8.176, p=0.004; χ^2=9.013, p=0.004; χ^2=4.393, p=0.036, respectively) and between subgroup III and non-ACEI group in hemoglobin level, hematocrit and MAP (χ^2=4.525, p=0.033; χ^2=4.317, p=0.038; χ^2 = 8.733, p=0.003, respectively).

Discussion

The influence of ACEI treatment on anemia parameters in HD patients receiving ESA was evaluated in this analysis. Usage of ACEI is justified in patients with CKD, considering it is a state clearly associated with cardiovascular (CV) events. ACE inhibitors antihypertensive treatment benefits cardiac remodeling, vascular stiffness, pulse wave velocity (22), left ventricule hypertrophy, oxidative stress and endothelial cell dysfunction (17-19). However, renin-angiotensin system blockers may hasten the progression to ESRD and cause the problems with hyperkalemia, despite their verified benefit in CKD. Therefore, underuse of RAS blockers in the most advanced CKD patients results in a lack of cardioprotection (23).

Mechanical damage to erythrocytes and blood loss can occur during dialysis (24). Additionally, uremic toxins can damage erythrocytes and lead to the poor bone marrow response to ESA. Uremia causes changes in erythrocytes morphology by inducing moving phosphatidylserin content from its inner leaflet to its outer leaflet of membrane, which presents the stimulus to circulating macrophages to remove them (25, 26). The research by Gaweda et al. indicated that the maximum erythropoietic response was associated with Kt/V, when Kt/V was 1.4 or greater. Patients with the values of Kt/V lower than 1.2 had a decrease in the erythropoietic response (27). Negative correlation between erythropoietin dose and Kt/V index when Kt/V was below 1.33 and no correlation when it was above 1.33 were found in the investigation by Movilli et al. (28). We did not find a correlation between ERI and Kt/V index between the two groups, although we found a lower value of Kt/V index in patients receiving ACEI compared with the group on the other antihypertensive treatment.

Our data showed statistically higher values of blood pressure in patients receiving ACEI compared with patients on other antihypertensive treatment (Table 2). Additionally, anemia parameters in HD patients receiving ACEI were lower compared to HD patients receiving other antihypertensive treatment (Table 3). In patients with ESRD, cardiovascular structural and functional changes develop as a result of volume overload and flow overload which are enhanced in the presence of anemia. Compensatory mechanisms for anemia imply hemodynamic (increased cardiac output, lower afterload, increased preload, positive inotropic and chronotropic effects) and non-hemodynamic (increased erythropoiesis, increased oxygen extraction) processes. Hypoxia-stimulated chemoreceptors and increased sympathetic nervous system activity lead to increased heart rate. These changes are responsible for an abnormal increase in systolic blood pressure that consequently leads to the development of left ventricle hypertrophy (29). On the one hand, usage of ACEI has confirmed beneficial effect on left ventricular hypertrophy, cardiac remodeling, heart rate, arterial stiffness, but on the other hand they can antagonize the effect of ESA treatment. It worsens anemia, whose detrimental influence on cardiovascular system was outlined previously. In our research, we were not acquainted with anemia status and blood pressure values before the introduction of ACEI in treatment of HD patients, so it is difficult to discuss how these changes in blood pressure are related to treatment with ACEI.

In both groups of HD patients, ERI values were negatively correlated with the number of red blood cells, hemoglobin levels and hematocrit (Table 4). Since ERI is calculated from hemoglobin value, those negative correlations are logical results.

Several studies informed on antagonizing effect of ACEI on ESA treatment in hemodialysis patients (30-34). In our study, a low dose of ACEI did not show statistical difference in anemia parameters in comparison to HD patients receiving other antihypertensive treatment. However, medium and high ACEI doses showed statistically lower values of the number of red blood cells, hemoglobin levels and hematocrit in comparison to HD patients receiving other antihypertensive treatment (Table 5). There is no general agreement on mechanisms in what way ACEI may disrupt erythropoiesis. It is reported that AT II has a stimulatory effect on erythropoiesis. Binding of AT II to its receptors on smooth muscle cells activates Jak-2-kinase. Erythropoietin also binds a surface receptor and signals to the nucleus through the Jak-STAT pathway (35). Angiotensin II may stimulate erythroid proliferation directly, considering that AT1 receptors are present on erythroid progenitors. The effect of the erythropoietin signal transduction pathway or other erythroid growth factors that share Jak-2 kinase–mediated signal transduction pathways may be enhanced by AT II. Furthermore, ACEI increase plasma Ac-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline), a strong inhibi-tor of hematopoietic stem cells, by preventing the degradation of Ac-SDKP (36). Angiotensin-converting enzyme inhibitors increased Ac-SDKP levels by 5 to 6-times (37).

The research by Le Meur et al. (38) demonstrated that dialysis patients with higher Ac-SDKP levels required larger doses of recombinant human EPO. Nakamoto et al. indicated that usage of ACE inhibitors enlarges the weekly dose of erythropoietin in patients on continuous ambulatory peritoneal dialysis. The weekly dose of EPO required in the group receiving ACE inhibitors was significantly larger than that required in the group receiving AT II type I receptor blockers. Although, AT II type I receptor blockers group also required higher doses of EPO at the end of the study (39). Haemodialysis pa-tients treated with losartan required larger doses of EPO in the study conducted by Odabas et al. (40). Some investigations did not acknowledge this effect of inhibiton of the renin-angiotensin system (41, 42). Hayashi et al. speculated that inhibitory effect of ACE inhibitors may be apparent only when high dose of ACE inhibitors and low dose of EPO are administrated together to a haemodialysis patient (43). It is possible that any negative effect of ACE inhibitors to erythropoiesis can be overcome by high dosage of EPO.

Several limitations are apparent in this study. Owing to the fact that this is a cross-sectional a study, we did not follow changes across time in anemia parameters, ESA dosage and ACE inhibitors dosage. We calculated the ERI from single ESA and hemoglobin value, which did not provide the dynamics of erythropoiesis process. The level of erythropoietin, AT II levels and ACE activity were not measured, and they could present better perspective on pathophysiological mechanism of ESA resistance. Despite those limitations of our study, ACE inhibitors treatment could affect ESA response in HD patients. Therefore, an observational cohort study, which should include the all previously mentioned variables, should be conducted.

Conclusion

Our study demonstrates that ACE inhibitors treatment negatively correlates with anemia parameters in HD patients. Treating HD patients receiving ESA with ACE inhibitors should be conducted carefully. It is necessary to determine an adequate dosage of ACE inhibitors to provide satisfactory cardioprotection but not to jeopardize erythropoiesis.

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UTICAJ TERAPIJE ACE INHIBITORIMA NA PARAMETRE ANEMIJE KOD PACIJENATA NA HRONIČNOM PROGRAMU HEMODIJALIZE

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Inhibitori angiotenzin-konvertujućeg enzima (ACEI) često se propisuju bolesnicima sa hroničnom bubrežnom insuficijencijom (HBI) zbog njihovog povoljnog efekta na kardiovaskularni sistem. Nije u potpunosti razjašnjeno da li terapija ACEI-ma utiče na parametre anemije kod bolesnika na hemodijalizi (HD).

Cilj ovog istraživanja bio je ispitati povezanost između upotrebe ACEI i parametara anemije kod HD bolesnika koji dobijaju stimulišuće agense eritropoeze (ESA).

Ova studija preseka uključivala je 114 HD bolesnika podeljenih u dve grupe: grupu koja je primala ACEI i grupu koja je primala druge lekove (antagoniste kalcijuma, β blokatore) u svom antihipertenzivnom tretmanu. Prema ekvivalentnoj dozi ACEI, bolesnici su bili podeljeni u tri podgrupe: I podgrupa (niska doza ACEI <10 mg/dnevno), II podgrupa (srednja doza ACEI između 10 i 20 mg/dnevno) i III podgrupa (visoka doza ACEI >20 mg/dnevno).

ACEI grupa imala je statistički značajno niži broj crvenih krvnih zrnaca (RBC) (3.17±0.39 prema 3.33±0.29 mmol/L, p=0.016), nivo hemoglobina (98.68±12.06 prema 104.94±7.77 g/dL, p = 0.001) i hematokrit (29.35±3.45 prema 31.19±2.27, p = 0.002) u poređenju sa drugom grupom. Prema dozi ACEI, nisu postojale statistički značajne razlike između tri podgrupe u parametrima anemije i srednjem arterijskom pritisku (MAP). Statistički značajna razlika između subgrupe I i grupe bez ACEI bila je u vrednosti MAP (χ^2 = 5.143, p = 0.023). Statistički značajne razlike između subgrupe II i grupe bez ACEI nađene su u broju RBC, nivou hemoglobina, hematokritu i MAP (χ^2 = 4.980, p = 0.026; χ^2 = 8.176, p = 0.004; χ^2 = 9.013, p = 0.004; χ^2 = 4.393, p = 0.036, redom) i između subgrupe III i grupe bez ACEI u nivou hemoglobina, hematokritu i MAP (χ^2 = 4.525, p = 0.033; χ^2 = 4.317, p = 0.038; χ^2 = 8.733, p = 0.003, redom).

Naše istraživanje pokazuje da terapija ACE inhibitorima negativno korelira sa parametrima anemije kod HD bolesnika. Određivanje odgovarajuće doze ACEI, koja će obezbediti zadovoljavajuću kardioprotekciju, ali neće ugroziti eritropoezu, bi trebalo da bude terapijski cilj. *Acta Medica Medianae 2017;56(3):107-115.*

Ključne reči: *inhibitori angiotenzin-konvertujućeg enzima, anemija, hemodijaliza, eritropoetin, hipertenzija*