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ORIGINAL PAPER

Hemostatic Complications in Hemodialysis Patients

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Background. Disorder of hemostasis in hemodialysis patients is focused in two directions, towards the development of thrombosis and bleeding. Both complications make it difficult to treat and are life-threatening for the patient. Monitoring of hemostatic parameters, it is possible to detect the first changes in the coagulation system and correct the factors that lead to changes and thus prevent or stop the further development of complications.

Aim. To determine the hemostatic and dialysis parameters and their influence on the occurrence and development of complications.

Patients and methods. From a total of 175 patients, 46 had signs of hemorrhagic syndrome and 16 of them had thrombosis. Parameters of primary and secondary hemostasis were determined and vascular access of ultrasound was examined.

Results. In the patients with thrombosis D-dimer level was significantly higher and amounted to 4.18 mg / l, while AT III levels were decreased for 54%. Elevated level of APTT was significant for the patients who had bleeding. In 86% of patients with thrombosis, ultrasound findings correlated with findings of D-dimer. Both complications were more pronounced in the older age group above 46 years.

Conclusion. Hemorrhagic syndrome is a frequent complication of thrombosis. The level of D-dimer is directly correlated with ultrasound detection of thrombotic formation. Elevated levels of APTT was in direct correlation with bleeding. The development of complica-tions are affected by other factors, such as: age, access type, type of dialysis membrane, the blood flow. Frequent control of hemostatic parameters is essential for early detection of complications. In the event of changes in coagulation system, type and dose of anticoagulant should be corrected and introducing additional oral anticoagulants should be considered.

Keywords. *hemostasis, hemodialysis, thrombosis, hemorrhagic syndrome, D-dimer*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Hemodialysis (HD) is the most common form of treatment in the patients with permanent renal impairment. It is applied using hemodialysis apparatus as a highly sophisticated device, which ensures the quality of treatment, but carries the risk of many complications. The most common complications are related to disturbances in coagulation system.

Hemodialysis disorder is caused by impairment of integrity of the blood vessel wall and by exposure of subendothelium to the blood flow, resulting in an abundance of changes in coagu-lation system.[1] Accumulation of uremic toxins leads to the disorders in platelet activity and disturbance of adhesion, which increases the tendency toward bleeding . On the other hand, the HD process implies extracorporal circulation system, whereby the blood of patients are exposed to different materials, but significant thrombogenicity (needles, catheters, arteriovenous lines, chambers, membrane, dialysate), which leads to activation of hemostasis and increases the risk of thrombolytic complications. Other important factors that facilitate coagulation during HD are: reduced blood flow, high hematocrit, turbulent blood flow, a high degree of ultrafiltration, recirculation within the vascular access, transfusions during dialysis, intra dialysis hypotension.[2] Uremic patients have high prevalence of systemic inflammation of the endothelium of blood vessels, which significantly increases the state of hypercoagulability.[3,4]

Adequate vascular access is a high degree of trauma, which increases the risk of thrombosis.[5] High levels of serum fibrinogen is an independent risk factor for thrombosis of vascular approach. Thrombosis of vascular access are the main reason for hospitalization in 17 to 25% of hemo-dialysis patients.[6] HD patients have reduced levels or reduced activity of antithrombin (AT III).[7] The increased values of D-dimer are considered a risk factor for the increased ac-

Table 1. Haemostasis parameters with and without thrombosis

Parameters	Thrombosis	AS	SD	p-value
Erythrocytes	no	3,57	,54	**0,01**
	yes	3,28	,37	
Hematocrit valve	no	,34	,04	**0,045**
	yes	,32	,03	
Thrombocytes	no	204,12	64,43	**0,043**
	yes	242,50	124,33	
Coagulation time-Howell	no	164,65	62,06	**0,027**
	yes	129,38	38,55	
APTT	no	52,58	37,14	**<0,001**
	yes	40,56	5,87	
PT	no	18,71	30,92	**0,012**
	yes	12,45	1,24	
INR	no	1,59	2,55	**0,011**
	yes	1,07	,11	
TT	no	21,51	21,22	0,941
	yes	21,10	21,10	
Fibrinogen	no	3,24	,84	0,975
	yes	3,24	1,18	
D dimer	no	,91	1,06	**<0,001**
	yes	4,18	,88	
AT III	no	,81	,13	**<0,001**
	yes	,54	,11	

tivation of coa-gulation. In clinical observations, the level of D-dimer can be a valuable diagnostic sign of thro-mbosis.[8] It is a very sensitive indicator of fibrinolytic activity. Normal results of D-dimer exclude the existence of thrombosis and pulmonary embolism with the probability from 97 to 99.9% .[9] It is believed that erythropoietin, as a substitute for blood-transfusion during HD leads to milder changes in the coagulation system.[10]

During HD anticoagulant funds are applied, which is done to prevent activation of the coagulation system. However, a large number of patients show changes that are focused in two directions, towards the development of thrombosis and bleeding. Venous thromboses of a number of blood vessels through which venous access is provided , are more frequent in comparation to thrombosis of other blood vessels and to pulmonary thromboembolia. Thrombosis is one of the most common causes ofmorbidity and mortality in developed countries. It is considered a very serious complication, because it complicates treatment and may endanger the life of the patient. On the other hand, the clinical manifestations of hemorrhagic syndrome are com-mon, and bleedings are very important , which are hard to be detected because they are not visible, nor are they accompanied by laboratory and haemostatic tests . Disorders of coagulation are detected by the tests of primary and secondary hemostasis, and by specific tests, either.[11] The incidence of hemostatic complications in HD patients have been the subject of a number of research studies. Research has shown in many studies that hemostatic parameters are important predictors of the emergence and development of hemostatic complications.

PATIENTS AND METHODS

The cut study included all the patients with terminal renal impairment, who were treated by hemodialysis at the Department of Internal Clinic Center of Tuzla. Patients were of both sexes, aged 10-84 years, who were provided by adequate vascular access. Previously, the consent of Ethical Committee of UKC of Tuzla was provided to carry out this study.

In the methodological procedure they used personal, demographic, anamnestic, clinical, dialysis data and methods of laboratory and echo-diagnostics. Standard methods were used to analyze hemostatic parameters in the blood (platelet count, coagulation time, activated partial thromboplastin time APTT, PT prothrombin time, thrombin time TT, fibrinogen, D-dimer, antithrombin III AT), and laboratory parameters from blood (number of RBC and hematocrit value). The parameters were determined for all the patients before HD treatment due to regular application of anticoagulation during dialysis. Test of parameters was performed

Table 1. Haemostasis parameters with and without thrombosis

Parameters	Hemorrrhagic syndrome	AS	SD	p-value
Erythrocytes	no	3,51	,47	0,389
	yes	3,61	,70	
Hematocrit value	no	,34	,04	0,121
	yes	,35	,05	
Thrombocytes	no	204,04	54,05	0,272
	yes	217,70	108,41	
Coagulation time-Howell	no	138,53	35,22	**<0,001**
	yes	225,65	71,92	
APTT	no	38,47	5,71	**<0,001**
	yes	87,96	54,44	
PT	no	12,14	1,20	**0,007**
	yes	34,97	54,52	
INR	no	1,12	,88	**0,017**
	yes	2,72	4,33	
TT	no	15,70	7,67	**<0,001**
	yes	37,67	34,62	
Fibrinogen	no	3,30	,86	0,105
	yes	3,06	,87	
D dimer	no	1,09	1,37	0,063
	yes	1,54	1,47	
AT III	no	,79	,15	0,083
	yes	,75	,15	

in the Clinic for Blood Transfusion and Department of Medical Biochemistry, UKC Tuzla. For all the tests, venous blood without signs of hemolysis and lipemia was used. Samples were taken in Vacutainer system of vacuum tube that contained 3.8% Na-citrate as anticoagulant agent. Relationship of blood and anticoagulant was 10:1. Testing was done from citric plasma sample after centrifugation. Analyses were done with the equipment for testing of hemostatic disorders (Sysmex CA-1500). Hematological parameters were analyzed automatically from venous blood cell analyzer Sysmex. Echo-diagnostic was performed on ultrasound apparatus of LOGIQ 400 CL PRO Series Di-gital Triplex Ultrasound System Ver 5.01 (General Electric, Europe) with a multifrequency linear probe-7.5-10 MHz.

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS 18.0 (Chicago, IL, USA). The basic tests of descriptive statistics were made, showing a measure of central tedence and dispersion. Tests of each variable for belonging to a normal distribution were done, using Kolmogorov-Smirnoff test, and the histogram display. Quantitative variables were compared by t-test with correction for unequal variance. For variables that were not normally distributed, a non-parametric Mann-Whitney analysis was performed. Categorical variables were analyzed by X2-test and Fisher's exact test. Risk analysis to determine a relationship likely (Odds Ratio - OR) was calculated where applicable. Non-parametric correlation by Spearman was used in testing the presence of significant relationships among variables. Uni-variant binomial logistic regression was used to test the level of influence of individual variables on the presence of thrombosis and / or hemorrhagic syndrome. All statistical tests were carried out with the level of statistical probability of 95% ($p < 0.05$).

RESULTS

From a total of 175 respondents in the whole sample, 88 (50.3%) were males while the remaining 87 were females (49.7%). The average age of the sample was 57.49 (14.51) years and ranged from 10 to 84 years.

The median length of dialysis service was 5 years with a range of 2-10 years, and with a minimum of 1 and

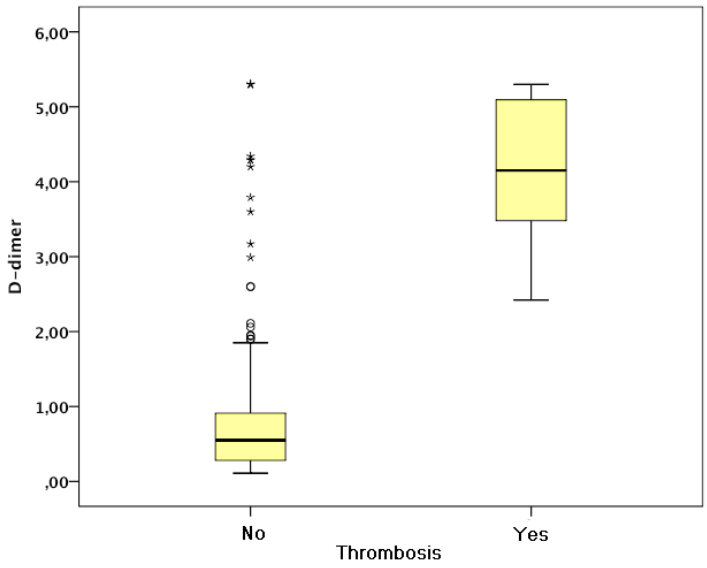

Figure 1. Comparison of D-dimer levels in patients with and without thrombosis

maximum of 31 years. Total 16/175 patients (9.1%) had thrombosis. We have compared the value of hemostatic parameters between the patients with and those without thrombosis. Tabular presentation is given in the Table 1.

Statistically significant differences are marked in bold print. A graphical representation of comparison of D-dimer levels in both groups was done Figure 1.

A total of 46/175 (26.3%) patients had clinical signs of hemorrhagic syndrome. We have compared the value of hemostatic parameters between the patients with and those without clinical signs of hemorrhagic syndrome. Tabulation of this comparison is given in the Table 2.

Statistically significant differences are highlighted in bold print, and the graphical representation on comparison of D-dimer levels between the two groups was given Figure 2.

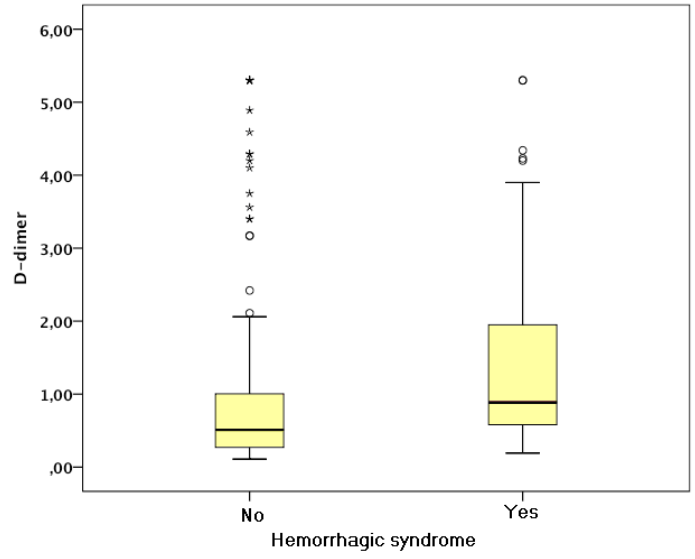

Figure 2. Comparison of D-dimer levels in patients with and without hemorrhagic syndrome

Significantly more patients with clinical signs of hemorrhagic syndrome was observed among subjects who had a CVC, and compared with those with AF ($X2 = 25.142$, $df = 1$, $p < 0.001$). Expressed in the level of risk, patients with CVCs compared to those with AF had a relationship likely to develop clinical signs of hemorrhagic syndrome of OR = 6.387 (95% CI = 3.047 to 13.388). The influence of certain variables on the presence of thrombosis was analyzed using logistic regression analysis. It is shown that the value of D-dimer is independent prognostic factor for thrombosis (OR = 3.862, 95% CI = 2.352 to 6.342, $p < 0.001$). AT III is a significant predictor of thrombosis ($p < 0.001$). The value of APTT had no significant predictive effect on the hemorrhagic syndrome (OR = 1.186, 95% CI = 1.103 to 1.276, $p < 0.001$).

DISCUSSION

Patients with permanent kidney damage have a number of complications in the system of blood coagulation such as bleeding, trombocyte dysfunction and deficit of coagulation factors. On the other hand, an important influence has the HD process itself, where the blood in the apparatus has a turbulent flow leads to the development of high pressure in blood vessels, leads to blood contact with dialysis membranes and preventive application of anticoagulant therapy.[12] This nonphisiological environment leads into the activation of platelets, leukocytes and the hemostatic cascade reaction. The end product of the reaction of the coagulation system are thrombin and fibrinogen.[13] The increased value of D-dimer is considered a risk factor for the development of thrombosis.[8] In the whole sample there was a proper distribution by sex and age. The largest number of respondents was in the age group of 46-55 years. In the total sample, 62 patients had complications and 46 patients showed signs of hemorrhage and 16 patients had developed thrombosis.

In the group of patients with thrombosis, higher levels of platelet and red blood cells and lower values of hematocrit were observed, compared to the group of the patients without thrombosis, which confirms the state of hypercoagulability. The values of D-dimer levels were elevated which represents a statistically significant difference. Yu et al [14] examined the hemostatic complications in HD patients and demonstrated that the value of D-dimer was significantly higher in the patients who had thrombosis. Duss et al [15] analyzed the fibrinolytic activity of the patients on HD with and without thrombosis and evidenced a statistically significant difference in the value of D-dimer in relation to the value measured in the group without thrombosis. Kano et al [16] examining the incidence of venous thrombosis showed a direct correlation between the value of D-dimer and ultrasound findings. Stolic et al [17] examined the incidence of thrombosis in the patients with arteriovenous (AV)-fistulas and proved that the value of D-dimer levels correlate with a given complication, and D-dimer is considered an important predictor of thrombogenicity. Significant differences in the level of AT III were ob-

served in the group of the patients with thrombosis and the deficit is considered a significant factor in the development of thrombosis. A large number of studies have shown similar results. Malyszko et al [10] examining the differences between the coagulation system of patients on hemodialysis and peritoneal dialysis have shown that the patients on HD have clearly expressed AT III deficiency, protein C and S. During the study, ultrasound showed 7 thrombosis in the patients with AV fistula and 9 thrombosis in the patients with central venous catheter (CVC). Out of the 16 proven thrombosis, in 14 cases (86%) the ultrasound findings correlated with findings of D-dimer. Also, 13 patients with thrombosis (81%) were in the older age group above 46 years. In literature many cases of thrombosis were described, which were caused by decreased blood flow through the device. The results of our study, 10 patients (62.5%) developed thrombosis of the lower blood flow through the device, less than 250ml/min while the other 6 patients (37.5%) in excess of 250ml/min. In all 16 persons who developed thrombosis, hemodialysis was conducted using low-flow (cellulose) membrane that can activate the coagulation compared to synthetic membranes.[18] In 46 cases, hemorrhagic syndrome was pronounced. The risk of bleeding was increased by inadequate dose of anticoagulation therapy. As for hemostatic parameters, changes in coagulation time, the values of APTT, PT, TT and D-dimer-a were observed. The value of APTT has represented a statistically significant difference of patients with hemorrhagic manifestations in relation to the group without events and was in direct correlation with the complications. The high value of D-dimer was notable in relation to the group without clinical manifestations, although these values were much lower in relation to thrombosis. This confirms the activity of fibrinolytic system in the group of patients with signs of hemorrhage. Yu et al [14] examining the impact of vascular access to the hemostatic complications in HD patients have emphasized significant fact that the value of D-dimer levels were elevated in the group with thrombosis and in the group of patients with signs of hemorrhage. In relation to vascular access, larger number of patients with a built-CVC had expressed signs of hemorrhagic syndrome in relation to the group of patients with AV fistula. 74% of patients were in the older age group above 46 years.

CONCLUSION

Hemorrhagic syndrome, as a complication of HD patients is much more common than thrombosis. Thrombosis is far more difficult to treat and is life-threatening for the patient. Significant haemostatic marker for both of complications is the increased value of D-dimer, but it is significantly higher in the group with thrombosis in a large percentage directly correlates with ultrasonographic findings. A significant factor for thrombosis is ATIII deficit, either. In the group of patients with hemorrhagic syndrome, a significant hemostatic marker was APTT. Both of these complications are more common in the age group above 46 years. Both complications are more frequent in the group of the patients with CVCs access. For the occurrence of thrombosis an important role has the low blood flow through the apparatus and low-flow dialysis membrane. As all the patients received anticoagulant therapy in the course of the HD treatment, so it remains an open question on types and doses of anticoagulants in comparison to developed complications. Frequent control of parameters of hemostasis, especially those significant for a particular complication, could be very useful in early detection and rapid reaction before its clinical manifestations. Also, in the case of early recognition of hemostatic changes the use of additional oral anticoagulants should be considered, in order to reduce the possibility of new complications, such as thrombosis of other blood vessels, pulmonary thromboembolism.

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