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Effect of Preoperative Activation Hemostasis on the Dynamics of Coagulation and Fibrinolysis Post Large Joint Arthroplasty

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Abstract

The prediction and diagnosis of thromboembolic complications in extensive orthopedic surgery pose a serious problem. Solving this problem becomes important in the study of the functioning of the hemostatic system. The study of the functioning hemostatic system is important for solving this problem. We investigated the effect of the pre-operative activity of fibrin formation and fibrinolysis on the dynamics of hemostasis, post primary hip or knee arthroplasty. This prospective study included 102 patients, segregated into two groups: The 1st group of 51 patients was characterized by the preoperative activity of the formation of fibrin degradation products (D-dimer) in the normal range (<250ng/mL) with a mean value of 153±55 ng/mL; the 2nd group of 51 patients had an initial D-dimer concentration above the norm, with a mean value of 470±201 ng/mL. Otherwise, the groups were equal with respect to gender, localization of the operated segment, and type of anesthesia. This study was performed prior to surgery, and days 1, 3, 7, 14, post arthroplasty. The coagulation parameters, fibrinolysis, and physiological anticoagulants were determined. Patients of the 2nd group were older than the patients of the 1st group: 51.7±9.7 years vs. 57.0±10.7 years, $p<0.05$. In the 2nd group, patients with higher initial levels of fibrin formation and lysis, showed retention of higher D-dimer concentrations after day 1 post surgery (1,447±478 ng/mL vs 1,202±594 ng/mL in the 1st group, $p<0.05$) and after day 3, post surgery. However, by day 7, the differences were leveled. No significant differences in the TAT, plasminogen and PAI-1 levels were observed during the entire study. No significant differences were noted in the number of verified thromboses of the deep veins, which was 17.5% in the 1st group and 16.1% in the 2nd group. The initial increase in the degree of fibrin formation and fibrinolysis did not raise the risk of thromboembolic complications during hip and knee arthroplasty. IJBM 2012; 2(3):186-191.

Key words: *D-Dimer, coagulation, fibrinolysis, large joint arthroplasty.*

Introduction

Most orthopedic surgeries are traumatic and accompanied by significant blood loss. They are also associated with an increased risk of thromboembolic complications, despite the availability of modern preventive anticoagulant therapy [1]. Therefore, the prediction and diagnosis of such complications poses a serious problem, particularly in the case of endoprosthesis of the hip and knee joints [2-4]. One way to solve this problem is to study the processes occurring in the hemostatic system, which controls

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both the formation and lysis of the thrombus.

The aim of this study was to investigate the coagulation and fibrinolysis processes during the total arthroplasty of hip or knee replacement taking into account the preoperative levels of hemo-coagulation activity.

Material and Methods

The study included 102 patients admitted to the clinic for primary hip or knee arthroplasty. Exclusion criteria were a history of pathology of the hemostatic system, uncontrolled blood pressure, kidney and liver failure, cancer, substance abuse, diabetes, rheumatoid arthritis, platelet count less than 100×10^9/L, anticoagulation therapy in the preoperative period, and the presence of documented thromboembolic events in patient history. The study was approved by the ethics committee, and all the patients signed informed consent.

The patients were segregated into two groups, based on the preoperative coagulation activity and fibrinolysis, levels of D-dimer, an insoluble fibrin degradation product which indicates the intensity of its formation and lysis. The 1st group (51 patients) included those patients with normal D-dimer concentration (<250 ng/mL), whereas the 2nd group (51 patients) included patients with a high D-dimer level. The group characteristics are presented in Table 1.

All the patients received low molecular weight heparin (enoxaparin), as antithrombotic prophylaxis medication. The first injection was given 12 hours prior to surgery, the second injection, 12 hours post arthroplasty, and finally, enoxaparin was administered one time per day at a dose of 40 mg, for two weeks. Prior to surgery and on the13-14th day post surgery, 40 patients of the 1st group and 31 patients of the 2nd group were subjected to an ultrasound duplex scanning of the leg veins.

Sampling for analysis was performed prior to surgery, 30 minutes after its completion and at the 1, 3, 7, 13-14th days, post arthroplasty. Venous blood was collected into a test tube to which was added 3.8% sodium citrate solution in 9:1 ratio. The parameters of plasma hemostasis were investigated in platelet-poor plasma (PPP), which was obtained by centrifuging the blood for 15 min at 3000 rev/min. To evaluate the coagulation system, activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and fibrinogen concentration based on the Clauss clotting technique on the CA-50 coagulometer (Sysmex) were determined using commercial kits from «Diagnostica Stago» and «Dade Behring». The thrombin formation activity was determined by the quantity of complexes «thrombin-antithrombin» (TAT) and their concentrations were examined employing the enzyme-linked immunosorbent assay (ELISA), using Enzygnost TAT kits («Dade Behring»). D-dimer as a marker of fibrinolysis and fibrin formation was measured by the ELISA reagent Asserachrom D-dimer («Diagnostica Stago»). The advantage of using this method was convincingly demonstrated by Stein et al [5]. The fibrinolysis system was also assessed by determining plasminogen, using the amidolytic technique with kits from «Technology Standard», and by determining the plasminogen activator inhibitor type 1 (PAI-1) using the ELISA method with kits from Technozym PAI-1 Actibind ELISA (Technoclone). The physiological anticoagulant antithrombin was studied using the amidolytic method with kits from «Technology Standard», while protein C, the other physiological anticoagulant, was determined by the ELISA method using Asserachrom Protein C (from Diagnostica Stago). Clotting tests and determination of antithrombin, and plasminogen were carried out within 2 hours after blood sampling. For ELISA testing the samples were frozen and stored prior to the study at -20°C. All studies were conducted following manufacturer's instructions, including the reagent and laboratory equipment manufacturers. The values of the parameters obtained were compared against the values of standard reference [6].

All the data was processed employing the variation statistical methods using the software Statistica for Windows 6.0. Analysis of the distribution of values obtained was performed using the Kolmogorov-Smirnov test. The mean (M) and standard error of the mean (m) were calculated. The Mann-Whitney (U Test) was used to compare the differences between the two independent groups (for nonparametric data). Spearman's rank correlation coefficient was also used. The value of p less than 0.05 was considered significant.

Table 1
Clinical characteristics of patients (M±SD)

Parameters	**1st group (n=51)**	**2nd group (n=51)**	**Significance of differences**
Age, years	51.7±9.7	57.0±10.7	p=0.035
Males/Females	22/29	21/30	NS
Hip arthroplasty/knee arthroplasty	36/15	37/14	NS
Type of anesthesia: • intravenous anesthesia+ventilation • combined spinal-epidural anesthesia	 21 30	 16 25	 NS NS
Time the surgery, min	156±44	150±51	NS

Note: *NS - not significant.*

Results and Discussion

In Table 2, the results of 102 patients are presented showing the parameters of coagulation and fibrinolysis systems, and physiological anticoagulants before arthroplasty and the dynamics during the postoperative period. The preoperative D-dimer concentration in the 2nd group was thrice the value of this index in the 1st group. The increase in the activity of fibrin formation and fibrinolysis was associated with older patient age (Table 1), which was consistent with earlier studies [7, 8]. However, the correlation analysis revealed a significant positive correlation between the D-dimer concentration and age, only in patients with normal D-dimer levels (r=0.33, p<0.05). In patients with elevated

Table 2
Dynamics of hemostasis parameters before and post the large joints arthroplasty in groups with different initial levels of fibrin formation and lysis (M±SD)

Parameters	Group	Prior to surgery	Post surgery				
			30 min	1st day	3rd day	7th day	14th day
D-dimer, ng/mL	1	153±55	1314±660*	1202±594*	837±348*	1383±427*	1171±336*
	2	470±201	1550±631*	1447±478*	1037±367*	1361±331*	1287±454*
Significance of differences		0.000	0.075	0.045	0.016	0.994	0.095
APTT,sec	1	31.9±3.1	34.6±4.7*	38.3±4.9*	35.4±4.7*	33.3± 4.0	34.1±4.5
	2	32.8±3.3	34.4±3.6*	36.9±4.7*	37.0±5.4*	34.9±4.7	34.9±3.4
Significance of differences		0.133	0.933	0.229	0.147	0.071	0.162
PT, sec	1	12.1±0.7	14.9±3.4*	14.7±1.1*	13.5±1.4*	12.3±0.7	12.6±1.0
	2	12.2±0.6	14.2±1.5*	14.7±1.2*	13.5±1.1*	12.6±0.6	12.9±0.8
Significance of differences		0.301	0.610	0.933	0.709	0.059	0.056
Fibrinogen, g/L	1	2.9±0,6	2.0±0.6*	3.0±0.8	6.2±1.8*	6.3±1.7*	4.9±1.4*
	2	3.4±0.9	2.4±0.7*	3.4±0.8	6.4±1.5*	6.0±1.5*	5.0±1.6*
Significance of differences		0.002	0.028	0.014	0.718	0.414	0.867
TT, sec	1	12.8±0.7	13.0±1.2	11.8±1.1*	12.6±1.4	13.4±1.8	13.7±1.3
	2	12.7±0.9	13.1±1.1*	12.3±1.3*	12.9±1.5	13.2±1.5	14.0±1.9
Significance of differences		0.590	0.611	0.143	0.276	0.793	0.867
TAT, ng/mL	1	4.4±4.4	30.0±16.2*	18.0±11.0*	14.5±9.8*	8.5±6.9*	7.9±6.4*
	2	4.5±3.2	35.4±16.0*	19.1±12.0*	13.0±9.1*	9.2±5.7*	8.1±4.4*
Significance of differences		0.344	0.141	0.497	0.278	0.356	0.411
Plasminogen, %	1	106.0±18.6	79.6±27.8*	74.2±15.6*	83.9±20.8*	115.9±19.5*	118.1±18.2
	2	106.1±16.7	77.9±16.0*	75.6±14.7*	84.9±15.2*	119.7±16.2*	116.4±11.3
Significance of differences		0.832	0.984	0.565	0.436	0.553	0.840
PAI-1,Units/mL	1	13.4±20.2	5.3±11.2	11.2±10.0	11.3±15.3	15.0±20.2	9.0±8.9
	2	14.7±21.0	6.4±12.0	15.0±17.0	13.0±17.2	11.4±11.2	10.7±20.2
Significance of differences		0.755	0.818	0.969	0.779	0.863	0.258
Antithrombin, %	1	103.9±13.2	72.7±11.6*	74.8±12.3*	90.5±14.2*	109.6±12.3*	105.5±14.0
	2	108.8±14.3	76.2±15.4*	80.7±12.2*	92.4±12.5*	109.0±13.6	107.6±13.5
Significance of differences		0.093	0.350	0.025	0.499	0.666	0.208
Protein C, %	1	90.8±14.0	69.0±15.2*	65.0±12.5*	79.2±9.5*	89.9±13.0	91.2±11.8
	2	89.0±15.1	73.6±17.5*	66.5±14.1*	77.1±12.6*	90.1±12.7	90.0±16.8
Significance of differences		0.645	0.428	0.855	0.702	0.784	0.593

Note: ** - p<0.05 (differences are statistically significant compared with the pre-operative parameters)*

levels of D-dimer formation, such a relationship was not observed (r=0.22), which indicated that it was irrespective of age-dependence in a significant activation of the coagulation process.

The initial formation of TAT complexes higher than the reference level in groups 1 and 2 indicates the increase in thrombin formation activity in both patient groups. However, if the 1st group experienced an effective slowing down of the coagulation process due to the anticoagulants at the time thrombin formation, thus maintaining the normal levels of fibrin formation, the 2nd group showed that the inhibition of coagulation occurred less efficiently, leading to the formation of a lot of fibrin. A little more active use of the physiological anticoagulants antithrombin and protein C in the first group confirmed this assumption. Determination of the Spearman correlation coefficients between the TAT and D-dimer showed no relationship between these parameters in the 1st group, that is, thrombin, which was formed in increasing amounts, was effectively inhibited by antithrombin III with the formation of the thrombin-antithrombin III complex in increased amounts, resulting in less fibrin formation. In the 2nd group, an association between TAT and D-dimer was found ($r=0.34$, $p<0.05$) which was linked to a reduction of the deterrent effect of the anticoagulants.

Coagulation parameters APTT and PT, which characterize the degree of coagulation by the internal and external factors, showed normal values prior to surgery in both groups, with no significant differences between them, indicating the total compensation of these factors at moderately elevated coagulation activity.

The preoperative hyperactivity of fibrinolysis, characterized by an increase in the plasmin degradation of fibrin forming D-dimer, was not associated with a lower plasminogen concentration. This could indicate an effective compensation of a higher consumption of the base proenzyme of the fibrinolysis system in the 2nd group. Lower fibrinolysis activity in the 1st group was not associated with the inhibition of the fibrinolytic process, as evidenced by the lack of significant differences in the PAI-1 activity, the main fibrinolysis inhibitor between the groups.

The patient group with the increased activity of fibrin formation and lysis at the time of admission to the clinic also showed a high concentration of substrate fibrin, which remained, however, within reference standards. A higher fibrinogen level could probably be a result of a severe inflammatory process, caused by osteoarthritis of the large joints, associated with the higher activity of the coagulation process [9]. No significant differences between the groups were noted regarding the speed at which fibrin is formed, from the thrombin time test.

Intraoperative damage to the bones, muscles, and blood vessels leads to a massive release of thromboplastin into the blood and powerful activation of thrombin formation in all patients. One day post arthroplasty, a significant decrease in the activity of TAT formation takes place. Subsequent gradual changes to the normalization of the indicator occurred within three weeks post surgery, with no significant differences between the groups. Contrary to the studies of Peternel et al., and Siemens et al. [10, 11], thrombinemia did not reach the initial level in both groups until the 14th postoperative day. This concurs with the data of Bunescu [12], which showed that the activation of coagulation persists for more than 10 days after primary hip arthroplasty.

As a result of the active intra-operative consumption of clotting factors and dilution with infusion solutions, the levels of the internal and external coagulation factors significantly dropped post arthroplasty in all patients, followed by their complete recovery in both groups by about 7 days post surgery.

Fibrin formation and fibrinolysis sharply increased post arthroplasty. During this period a significant correlation between the D-dimer concentration and TAT was noted in both groups: $r=0.44$, $p<0.05$ and $r=0.46$, $p<0.05$ for the 1st and 2nd groups, respectively, which indicates a significant dependence on the fibrin formation and fibrinolysis with thrombin formation at this time. On day 3, a significant shift towards the normalization of D-dimer formation was observed, although on the 7th postoperative day a marked re-increased fibrinolysis activity was seen, associated with the repair processes in the vascular wall [13]. This increase in fibrinolysis occurred against the backdrop of a significant reduction of thrombinemia, relative to the previous time point. The high level of fibrinolysis persisted until the end of the study. The dynamics of the D-dimer concentration reveals a similar pattern in both groups; however, on the 1st and 3rd days post surgery, a higher D-dimer concentration was found in the second group, which may indicate the dependence of fibrin formation and its lysis in a period when an increase in the fibrinolysis compensates for the increase in the coagulation process from the initial level. From the 7th day post arthroplasty, when the plasmin degradation of fibrin shows a predominantly reparative nature, this dependence is lost.

At the end of the operation, the consumption of plasminogen dramatically increased, and consequently its level decreased significantly, remaining low, until 3 days post surgery. By the 7th day, recovery of plasminogen occurred with a significant excess of the initial level, which created a reserve for the effective implementation of the reparative lytic processes. Until the end of the observation period, the plasminogen activity did not differ from the preoperative level. The dynamics of the plasminogen activity in both groups showed no significant differences during the study period, which could indicate the adequacy of the level of this proenzyme. Determination of Spearman correlation coefficients between the plasminogen activity and D-dimer concentration in both groups showed no significant association between these indicators, which could also indicate a lack of restriction of the fibrinolysis du to the plasminogen levels.

The activity of PAI-1, the primary inhibitor of fibrinolysis, dropped post arthroplasty by 60.3% in the 1st group and by 56.3% in the 2nd group. This was due to its heavy consumption in the process of compensatory inhibition of activated fibrinolysis. After the 1st day post surgery, the activity of PAI-1 increased significantly with respect to the postoperative levels but had no significant differences from the baseline values in both groups. There were no differences with regard to the preoperative activity at subsequent time points of the study. It should be noted that the significantly

lower level of the products of fibrinolysis in group 1 was not associated with a higher PAI-1 activity. Correlation analysis revealed no significant relationship between D-dimer concentration and PAI-1 activity during the entire observation period. Thus, the decreased production of D-dimer in a group cannot be explained by the lower activity of fibrinolysis, rather by the lower production of fibrin.

The antithrombin III and protein C levels significantly dropped post surgery in both groups, due to the intraoperative dilution with infusion solutions and the active consumption of anticoagulants. One day post surgery, antithrombin showed significantly lower levels in the 1st group when compared with the 2nd group, which could be attributed to the more intensive use of the anticoagulant, leading to decreased fibrin formation and lysis when compared with the 2nd group. It is interesting to note that within the groups there was a significant negative correlation between the activity of antithrombin III and D-dimer concentration : r=-0.37, $p < 0.05$ and r=-0.42, $p<0.05$ for the 1st and 2nd groups, respectively, i.e. at a lower level of anticoagulant activity there is a higher fibrin formation. By the 7th day, the levels of the physiological anticoagulants, AT and protein C, were completely restored, and their activity showed a close value until the end of the study.

At the end of the surgery, the concentration of fibrinogen significantly decreased, but on the 1st day after surgery, its level did not differ from the original value. During the 1st postoperative day, the fibrin substrate concentration was significantly higher in patients who showed an initially higher concentration of this protein. The fibrinogen level, therefore, appears to have a significant impact on the amount of blood loss during surgical trauma [14, 15]. This accounts for the smaller volume of blood loss within one day post surgery in the 2nd group than in the1st group (1478±93 mL/day and 1340±71 mL/day, respectively), which can be explained by the higher concentration of the substrate of fibrin formation. On the 3rd day a significant increase in the fibrinogen, as the protein of the acute phase of inflammation, is noted. On the 5-7th days post surgery, hyperfibrinogenemia was more pronounced in the 1st group. This, perhaps, was a result of the decreased synthesis of the acute phase protein, in patients of the older age groups.

Ultrasound duplex scanning of the leg veins was performed in all patients prior to surgery, on the 13th and 14th days post the arthroplasty in 40 patients of the 1st group and in 31 patients of the 2nd group. Prior to surgery, no marked thromboembolic complications were visible in any of the patients surveyed. However, deep vein thrombosis was revealed during the postoperative period in 7 of the 40 patients (17.5%) of the 1st group and in 5 of the 31 patients (16.1%) of the 2nd group. Contrary to the findings by Corradi et al., [16] and similar to the study by Chotanaphuthi et al. [17], we found no relationship between the baseline D-dimer concentration and the development of thrombotic complications in patients post primary hip or knee arthroplasty.

Conclusion

Increased D-dimer concentrations in patients admitted for reconstructive hip or knee surgery were found associated only with those in the older age group. At baseline, the higher levels of fibrin formation and fibrinolysis are stored during days 1 and 3, post surgery; however, it does not significantly affect the development of deep vein thrombosis. In a normally functioning system of fibrinolysis, and the absence of thrombotic history and additional risk factors, the initial increase in D-dimer concentration cannot of itself be a predictor of the increased risk of thromboembolic complications in hip and knee arthroplasty.

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