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Effect of preoperative platelet alpha-granules secretion on hemostasis and blood loss in large joint arthroplasty

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Abstract

Background. Currently, it was proven that the role of platelets is not limited to the formation of a clot that stops blood loss and provides vascular wall repair. The importance of determining the functional characteristics of platelets in patients who underwent traumatic surgery is beyond doubt. However, there are few studies on this subject.
Aim. To determine the effect of the preoperative platelet α-granules secretory activity on the coagulation parameters and blood loss in total hip arthroplasty (THA).
Material and methods. The study included 58 patients admitted to the hospital for primary total hip arthroplasty. All patients were divided into 2 groups according to the preoperative plasma level of the specific platelet α-granules protein β-thromboglobulin (β-TG). The group with a low plasma level of β-thromboglobulin (<30 IU/ml) consisted of 30 patients, the group with a high level (≥30 IU/ml) — 28 patients. Blood sampling was carried out 1 day before the operation, 30 minutes after surgery, on the 1st, 3rd, 7th 14th days after the total hip arthroplasty. The platelet count, β-thromboglobulin, and D-dimer levels were determined. The plasma coagulation was examined by using thromboelastography. The volume of intraoperative blood loss was estimated by the gravimetric method, postoperative blood loss — by drainage volume. Statistical analysis was carried out by using the Friedman, Wilcoxon, Mann–Whitney tests, calculating Spearman's rank correlation coefficient. All calculations were performed using the Statistica 8.0 software.
Results. Before surgery, the group with a high level of β-thromboglobulin showed significantly higher levels of D-dimer than the group with low levels: 132 [73; 191] ng/ml and 79 [37; 123] ng/ml (p=0.024); and shorter R times (time to onset of clotting): 13.7 [11.5; 15.3] min and 15.5 [13.0; 18.1] min (p=0.048), respectively. The maximum β-thromboglobulin was observed at the end of the operation. The release of β-thromboglobulin was significantly more intense in the group with low levels of β-thromboglobulin than in the group with high levels: 35.6 [10.5; 78.0] IU/ml and 19.0 [0; 41.3] IU/ml, respectively (p=0.027). A relationship was found between β-thromboglobulin levels and D-dimer concentration early after surgery (30 minutes), Spearman's correlation coefficients for groups with low and high levels of β-thromboglobulin: r=0.57 and r=0.48, respectively (p <0.05 for both). Blood loss in the group with low β-thromboglobulin levels was significantly higher than in the group with high levels: 850 [550; 1050] ml and 600 [500; 850] ml, respectively (p <0.05).
Conclusion. In patients requiring total hip arthroplasty, an increase in the activity of platelet α-granules secretion is associated with an increase in the activity of fibrin formation and a shortening of reaction time to onset of clotting; during surgery, the secretory activity of platelets is directly related to the activity of coagulation and affects blood loss volume.
Keywords: platelets, β-thromboglobulin, total hip arthroplasty (large joint replacement).

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Background

The role of platelets has now been proven to be not limited to the formation of a clot that stops blood loss and enables repair of the vascular wall [1]. Platelets are also recognized as key effector cells involved in the regulation of immunological reactions and inflammation [2, 3]. In extensive orthopedic surgeries associated with insertion of an implant, such as hip arthroplasty (HA), the role of platelets is especially important, since it is necessary not only to cope with the consequences of massive vascular damage but also to create conditions for effective osseointegration of the prosthesis [4].

By interacting with both the subendothelium and implant, platelets are quickly activated and release the contents of their granules. The three main types of platelet granules are α-granules, dense granules, and lysosomes [5]. Their timely release is required for an adequate effective response of the body to extensive surgery [6]. The secretion of granules is critical not only for the regulation of the "canonical" functions of platelets, as the components of the granules mediate the action of platelets on other cells [5].

The most numerous α-granules of platelets are those that store factors that promote platelet activation (such as von Willebrand factor and fibrinogen), coagulation (such as factors V, XI, and XIII and prothrombin), anticoagulation (such as tissue factor pathway inhibitor and protein S), fibrinolysis (such as plasminogen and plasmin) [7]. α-granules contain adhesive receptors, that is, from half to two-thirds of the total αIIbβ3-platelet receptor for fibrinogen, and more than a third of the GPVI receptors for collagen, which are transferred to the surface of the platelets after their activation, enhancing further the adhesive–aggregation properties [8]. α-granules also contain growth factors and cytokines that control regenerative processes and promote tissue repair and implant stability [9, 10].

One of the specific platelet proteins is β-thromboglobulin (β-TG), which is an intermediate product of proteolysis of the platelet basic protein. β-TG has a pronounced chemoattractive activity and stimulates the migration of fibroblasts and neutrophils to areas of inflammation and vascular damage [11]. This protein is recognized as a marker of platelet factor secretion from α-granules [12, 13].

Platelets circulating in the blood are heterogeneous. Factors that determine heterogeneity may be different between megakaryocytes and aging platelets. In addition, circulating platelets are under the activating and inhibitory influence of various biomolecules and biomechanical conditions of blood flow. These effects modulate the response of platelet to subsequent stimulus, i.e., positive or negative platelet priming occurs [14, 15].

Endoprosthetics of large joints is a traumatic surgery associated with a high risk of both significant blood loss and thromboembolic complications [16, 17]. The importance of determining the functional characteristics of platelets in patients undergoing such surgeries is beyond doubt; however, only a few works have focused on this problem.

In this regard, this **work aimed to** determine the effect of the preoperative level of secretory activity of α-granules on changes in hemostasis parameters and blood loss volume during HA.

Materials and methods of research

The study included 58 patients admitted to the hospital for primary HA. The inclusion criteria were age 40–75 years and stage III–IV coxarthrosis. The exclusion criteria were chronic diseases in the stage of decompensation, disorders of the hemostatic system, and intake of anticoagulant or antiplatelet drugs within 2 weeks before surgery.

The work was approved by the local committee on biomedical ethics of the V.D. Chaklin Ural Institute of Traumatology and Orthopedics (Protocol No. 6 dated July, 03, 2011).

All patients underwent HA. All patients included in the study received standard anticoagulant prophylaxis with low-molecular-weight heparin, sodium enoxaparin. The anticoagulant was administered subcutaneously at a dose of 40 mg/day for 14 days after surgery.

Blood samples for analysis were taken from a vein in the morning 1 day before surgery, at the end of surgery (after 30 min), and on days 1, 3, 7, and 14 after HA. To determine the platelet count, blood was collected into test tubes with potassium salt of ethylenediaminetetraacetic acid. For thromboelastographic studies, blood was taken into test tubes with 3.8% (0.129 M) sodium citrate solution in a standard ratio of 1:9 with respect to the blood taken. To determine β-TG, blood was taken in STAD tubes in the same ratio of blood and anticoagulant. Platelet-poor plasma was obtained by centrifugation at 3000 rpm for 15 min. For subsequent enzyme immunoassay, blood plasma samples were frozen and stored at –20°C.

The platelet count was determined in whole blood using a Cell-Dyn 170 hematology analyzer (Abbott Laboratories, USA). Thromboelastographic studies were performed on a TEG-5000 computerized thromboelastograph (Haemoscope Corporation, USA), and reaction time (R) and maximum amplitude (MA) values were determined. R is the reaction time from the start of sample analysis to reaching the level of clot detection, and the R value

Table 1. Characteristics of patients who underwent hip arthroplasty and had low and high initial levels of β-thromboglobulin

Indicator	LTG group	HTG group	p
Age, years[1]	59.4 ± 11.2	58.8 ± 9.6	0.663
Gender, men/women, n	12/18	14/14	0.617
Type of anesthesia, general/regional, n	8/22	5/23	0.299
Prosthesis type, cemented/cementless, n	11/19	7/21	0.638
Surgery time, min[1]	116 ± 25	119 ± 24	0.817

Note: [1]Results are presented as mean ± standard deviation; LTG, group with a low level of β-thromboglobulin; HTG, group with a high level of β-thromboglobulin.

decreased under hypercoagulation. MA characterizes the maximum strength of the formed clot; under physiological conditions, it is the result of the action of two components, a moderate contribution of fibrin and the most significant contribution of platelets [18].

β-TG activity was quantified by enzyme immunoassay using Asserachrom β-TG kits (Diagnostica Stago, France). Calibration solutions were obtained by serial dilution (1, 1:2, 1:4, 1:8, and 1:16) of commercial standard plasma. Quality control was performed at low and high levels.

D-dimer is a specific product of cross-linked fibrin degradation during its plasmin degradation. It serves as one of the most important markers of activation of the coagulation and fibrinolytic systems. D-dimer was determined by enzyme immunoassay using Technozym D-dimer enzyme-linked immunosorbent assay reagents (Technoclone, Austria).

The volume of intraoperative blood loss was determined gravimetrically, and postoperative blood loss was determined as blood loss through drains.

To establish the effect of the preoperative level of secretion from α-granules on the postoperative activity of their release, coagulation, clot formation parameters, and blood loss volume, all patients were distributed into two groups according to the preoperative level of β-TG release. The low β-TG (LTG) group consisted of 30 patients with blood β-TG levels <30 IU/mL, and the high β-TG (HTG) group consisted of 28 patients with β-TG levels of ≥30 IU/mL.

The characteristics of the groups are presented in Table 1. They did not differ in age, gender, type of prosthesis used, type of anesthetic aid, and time of surgical intervention.

Data obtained were processed in accordance with the rules of variation statistics using Statistica 8.0. The nature of the distribution of variation series was evaluated using the Kolmogorov–Smirnov test. When studying the change in indicators, the Friedman test was used. Comparison with the initial value was performed using the Wilcoxon test. The indicators between the studied groups were compared using the Mann–Whitney test. To assess the relationship between indicators, correlation analysis was used with the calculation of the Spearman coefficient. Differences were considered significant at $p < 0.05$.

Results and discussion

The concentration of β-TG before HA and in the postoperative period revealed that the reaction of platelets to surgery is stereotyped, but differs in severity in cells with different initial activities. The maximum level of this protein was registered immediately after the surgery. Starting from day 1, the amount of β-TG in the blood gradually decreased in both groups (Fig. 1). However, in the LTG group, the β-TG concentration remained at an elevated level relative to the initial level until the end of the follow-up period ($\beta\text{-TG}_{in}$ = 22.4 [17.7; 26.6]; $\beta\text{-TG}_{day14}$ = 31.0 [27.7; 43.4], $p_{\beta\text{-TGday14} - \beta\text{TGin}}$ = =0.0001, Wilcoxon test), whereas in the HTG group, it returned to preoperative values ($\beta\text{-TG}_{in}$ = =40.0 [34.2; 61.5]; $\beta\text{-TG}_{day14}$ = 41.5 [31.7, 61.0], pβTG14day – βTGref = 0.581, Wilcoxon test 5 [31.7; 61.0], $p_{\beta\text{-TGday14} - \beta\text{TGin}}$ = 0.581, Wilcoxon test).

A similar pattern of changes in the marker of platelet secretion was noted in both groups. However, in the LTG group, the severity of these changes relative to the initial level demonstrated significance (Friedman's test, $p = 0.0001$). However, in the HTG group, the changes are less pronounced (Friedman's test, $p = 0.269$) (Fig. 1).

In the case of a low preoperative level of platelet secretion, the release of β-TG during surgery was significantly more intense than with a high preoperative level of the release of this protein, namely, 35.6 [10.5; 78.0] IU/mL and 19.0 [0; 41.3] IU/mL in the LTG and HTG groups, respectively ($p = 0.027$).

As a result of the differences in the secretion of β-TG in response to surgery after HA, this protein level in the blood in both groups level out. The leveling of β-TG concentrations in both groups after surgery can be explained by the limited pool of this protein in the granules and the comparable number of all patients included in the study, where-

as the differences concerned only the method and rate of its release.

A previous found that the kinetics and degree of platelet exocytosis vary [19]. In their recently published work, Karolczak et al. (2021) showed that α-granule proteins can be released in different ways for different periods [20].

Starting from day 1 after surgery, with a gradual decrease in the blood concentration of β-TG, the differences between the groups become significant again (Fig. 1). This may indicate the preservation of the initial platelet heterogeneity even after a powerful surgical effect on the body. The limitation of this study is the inability to establish whether this heterogeneity is associated with genetic factors or with the characteristics of the disease course, which requires further research.

In our study, the intensity of platelet secretory activity did not depend on gender and age (Table 1). For patients with severe hip osteoarthritis, the severity of the pathology appears to be the major factor in determining the degree of positive platelet priming. This finding is consistent with the data obtained by Savage et al., who demonstrated that differences in the content of platelet α-granules were not due to age-related changes [21], and by Weibrich et al., who showed that neither age nor gender affects the levels of release of growth factors produced by platelets [22].

The efficiency of the reparative regeneration after tissue injury, including after major surgical interventions, is largely determined by the presence of an optimal level of growth factors and molecules that ensure the involvement, proliferation, and differentiation of stem cells [23]. Platelet α-granules contain all the major growth factors; thus, it is important to know the level of secretion from these granules, not only during clot formation, but also in the later postoperative period. Our study showed that the increased level of secretion persists for at least 2 weeks after surgery (Fig. 1).

The activity of postoperative release of α-granules is largely determined by the initial activity of secretion, which suggests the possibility of determining specific platelet proteins to predict the course of repair processes in major orthopedic surgical interventions.

The changes in the count of circulating platelets after HA differ from the changes in β-TG secretion (Fig. 2).

The platelet count decreased in the early postoperative period and increased starting from postoperative day 7 (Friedman's test, $p < 0.001$ for both groups). Before surgery, no significant differences were found between the groups. In the early postoperative period, a higher platelet count was registered in the HTG group. Starting from day 1, again, the platelet count in the blood was not significantly different between the groups (Fig. 2). No correlation was found between the platelet counts and β-TG levels in the blood at any time points.

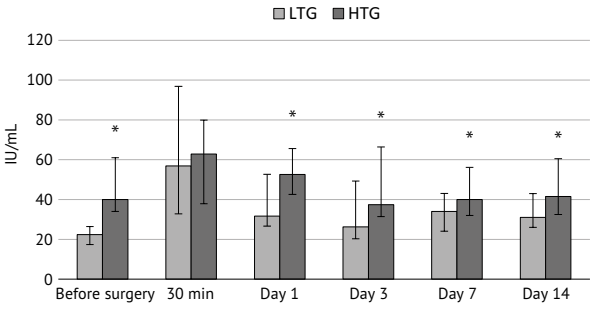

Fig. 1. Blood concentration of β-thromboglobulin in hip arthroplasty. Results are presented as median [interquartile range]; *Differences between the groups are significant ($p < 0.05$, Mann–Whitney test); LTG, low β-thromboglobulin group; HTG, high β-thromboglobulin group.

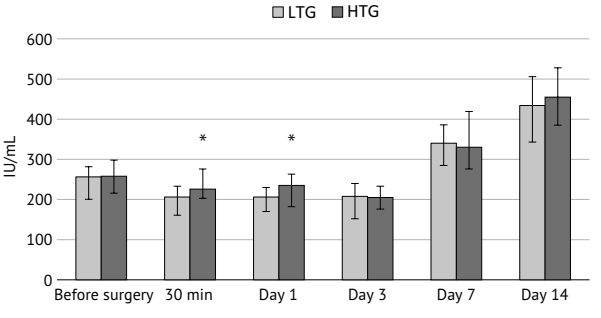

Fig. 2. Blood concentration of platelets during hip arthroplasty. Results are presented as median [interquartile range]. *Differences between the groups are significant ($p < 0.05$, Mann–Whitney test); LTG, low β-thromboglobulin group; HTG, high β-thromboglobulin group.

Thus, the level of secretion of β-TG by platelets, neither before nor after HA, is related to their count. The absence of a relationship between the platelet count and blood concentration of β-TG confirms the statement that different people have different population range of platelets with different secretory activities and degree of activation in response to pathological effects. In both normal and pathological conditions, studies have proven that platelet populations with different response ranges in hemostatic and vascular processes can be distinguished [14, 15].

The initial increase in the concentration of β-TG in the blood was associated with an increased level of the fibrin generation marker D-dimer, as well as with the rate of the latent period of blood clot formation, which is reflected by the thromboelastographic index R (Table 2). The association of a higher initial concentration of β-TG with a higher level of D-dimer, which indicates the activity of fibrin formation, and with the rate of the initial stage

Table 2. Coagulation parameters before and after hip arthroplasty

Parameter	Group	Before surgery	After surgery				
			After 30 minutes	Day 1	Day 3	Day 7	Day 14
D-dimer, ng/mL	LTG	79 [37; 123]	945 [488; 1496]	1025 [500; 2380]	364 [266; 648]	1540 [1111; 2232]	1650 [1018; 2448]
	HTG	132 [73; 191]*	1020 [505;1815]	1202 [612;1589]	408 [266; 644]	1430 [842; 2483]	1995 [1061; 576]
	p	0.024	0.655	0.957	0.875	0.728	0.398
R, min	LTG	15.5 [13.0; 18.1]	12.9 [9.3; 16.5]	15.1 [12.4; 20.2]	14.1 [9.6; 19.0]	15.1 [11.2; 21.2]	17.1 [12.5; 20.0]
	HTG	13.7 [11.5; 15.3]*	11.7 [9.7; 15.1]	13.0 [10.7; 16.2]	11.7 [9.6; 15.3]	12.5 [9.2; 17.8]	17.0 [10.1; 22.3]
MA, mm	LTG	56.5 [51.0; 59.4]	57.6 [52.5; 59.9]	61.2 [58.7;64.8]	70.1 [66.5; 73.0]	70.6 [68.8; 73.3]	67.7 [63.0; 72.2]
	HTG	54.2 [49.9; 59.2]	57.8 [52.2; 60.0]	59.0 [56.5; 62.0]	66.3 [64.0; 70.3]	71.6 [67.8; 73.2]	68.0 [63.8; 71.1]
	p	0.048	0.555	0.327	0.234	0.237	0.900

Note: Results are presented as median [interquartile range]. *Differences between groups are significant ($p < 0.05$, Mann–Whitney test). LTG, group with a low level of β-thromboglobulin; HTG, group with a high level of β-thromboglobulin.

of the blood coagulation process, indicates a significant relationship between the preoperative activity of secretion of α-granule components by platelets and coagulation activity in the patients.

Surgery induces a powerful activation of the coagulation process even in the presence of anticoagulants [24]. In this study, we also found a sharp increase in the blood concentration of D-dimer (Friedman's test, $p < 0.001$), decrease in the latent period (until the detection level is reached) of blood clot formation (thromboelastographic index R, Friedman's test, $p < 0.05$), and increase in clot density (MA thromboelastographic index, Friedman's test, $p < 0.05$) (Table 2). In the postoperative period, differences were noted in these parameters between the groups; however, no significant difference was noted; perhaps this was due to their significant variability.

The high variability of the D-dimer concentration can be due to the fact that this indicator reflects two processes, generation and its plasmin degradation [25]. The variability of thromboelastographic parameters also appears to be determined by the multifactorial influence on the parameters of clot formation [18].

A correlation between the β-TG level and D-dimer concentration in the blood was found in the earliest postoperative period (30 min after surgery); thus, Spearman's correlation coefficients in the LTG and HTG groups were $r = 0.575$ ($p < 0.01$) and $r = 0.481$ ($p < 0.02$), respectively. No significant correlation was found between the platelet count and blood concentration of D-dimer, and Spearman's correlation coefficients in the LTG and HTG groups were $r = 0.065$ and $r = 0.187$, respectively.

Moreover, at the end of surgery, a correlation was found between the platelet count and MA index, and Spearman's correlation coefficients in the LTG and HTG groups were $r = 0.391$ ($p < 0.05$) and $r = 0.467$ ($p < 0.04$), respectively.

Correlation analysis data help conclude that in the early postoperative period, the amount of fibrin generated is more related to the intensity of the release of granule components, whereas the strength of the emerging fibrin matrix will be largely determined by the platelet count.

The presence of an association between the activity of fibrin generation and the level of a specific component of α-granules, and the parameters of clot strength, with the platelet count, which we revealed in the early postoperative period, indicates the importance of both the count and functional activity of platelets for the effective formation of clots, which not only stop blood loss, but also serve as the primary matrix for the regeneration process [26].

Comparison of intraoperative blood loss in the two groups of patients showed that the blood loss volume was higher in the LTG group than in the HTG group, namely, 350 [250; 550] mL and 250 [200; 400] mL, respectively ($p = 0.031$). Total blood loss was also higher in the LTG group than in the HTG group, with 850 [550; 1050] mL and 600 [500; 850] mL, respectively ($p = 0.041$).

The initial platelet count was similar in both groups. However, in the HTG group, their preoperative activation with the release of α-granule components was higher. It can be assumed that in patients requiring HA, preoperative positive platelet priming, together with increased coagulation activity, leads to a partial depletion of the secretory pool of circulating platelets with the release of α-granule components into the bloodstream and creates more favorable conditions for the urgent formation of clots under conditions of massive vascular damage during surgery and ensures less blood loss.

Conclusions

1. In patients requiring total hip replacement, the coagulation potential of the blood is directly

related to the activity of releasing platelet α-granules; with increased secretion, the activity of fibrin formation increases, and the latent period of clot formation decreases.

2. During HA, the level of a specific protein of platelet α-granules β-TG correlates with the duration of the latent period of clot formation and the intensity of fibrin generation. The intensity of the secretory activity of platelets affects the amount of blood loss.

3. The postoperative activity of the release of α-granules is dependent on the initial level of secretion. The levels of main growth factors in these granules suggests the possibility of predicting not only blood loss but also the course of the repair process using platelet markers in patients requiring large joint replacements, which necessitates further research.

Author contributions. I.P.A. planned, collected, and analyzed the results. B.G.Yu. planned, analyzed, and discussed the results. S.M.K. was the work supervisor.

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Conflict of interest. The authors declare no conflict of interest.

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