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Changes in indicators of the coagulation system and markers of inflammation in the blood of patients with degenerative diseases of large joints in the case of total arthroplasty

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Predicting the risk of developing thrombotic complications is an extremely important task when planning total arthroplasty of large joints (TAJ). Objective. Based on the retrospective analysis of the results of the biochemical examination of patients with degenerative diseases of large joints before and after TAJ, determine the changes in the markers of the hemostasis system and inflammatory processes, which are the most informative for the preoperative prediction of the development of hypercoagulable conditions. Methods. In the blood serum of 39 patients with degenerative diseases of the hip and knee joints of III–IV stages according to Kellgren–Lawrence before and after TAJ, the following were investigated: prothrombin time, international normalized ratio (INR); the content of fibrinogen, soluble fibrin-monomeric complexes (SFMC), D-dimer, antithrombin III, glycoproteins (GP), sialic acids, C-reactive protein (SRP), seroglycoides, haptoglobin; activated partial thrombin time (APTT), fibrinolytic activity (FA). The control group consisted of 30 practically healthy donors. The results. Before TAJ, the serum content of GP patients was 28.80 % higher than the control indicators; haptoglobin — by 20.00; CRP — 82.88; SFMC — 33.60; fibrinogen — 60.32; D-dimer — 41.04 %. The INR was reduced by 25.40 %, the content of antithrombin III — by 21.90 %, FA slowed down by 63.00 %. After TAJ, the content of total HP in the blood serum ofpatients exceeded the indicator of the control group by 55.80 %, sialic acids by 35.60 %; seroglycoides — 55.26; haptoglobin — 61.42; CRP — 151.33 %. An additional reduction of 10.58 %, prothrombin time, APTT — by 15.40 %, antithrombin III activity — 19.10 %, increase in fibrinogen content — 34.90 % was observed; D-dimer — 25.10; SFMC — 36.18; prolongation of FA time — by 29.30 %. Conclusions. To prevent the development of thrombophilic conditions after TES, it is necessary to monitor the most informative markers: increase in FA time, content of fibrinogen, D-dimer, SFMC and haptoglobin.

Прогнозування ризику розвитку тромботичних ускладнень є вкрай важливим завданням під час планування тотального ендопротезування великих суглобів (ТЕС). Мета. На підставі ретроспективного аналізу результатів біохімічного обстеження пацієнтів із дегенеративними захворюваннями великих суглобів до та після ТЕС визначити зміни маркерів системи гемостазу та запальних процесів, найбільш інформативні для передопераційного прогнозування розвитку гіперкоагуляційних станів. Методи. У сироватці крові 39 пацієнтів із дегенеративними захворюваннями кульшового та колінного суглобів III–IV стадій за Kellgren–Lawrence до та після ТЕС досліджено: протромбіновий час, міжнародне нормоване відношення (МНВ); вміст фібриногену, розчинних фібрин-мономірних комплексів (РФМК), D-димеру, антитромбіну III, глікопротеїнів (ГП), сіалових кислот, С-реактивного протеїну (СРП), сероглікоїдів, гаптоглобіну; активований частковий тромбіновий час (АЧТЧ), фібринолітичну активність (ФА). Контрольну групу склали 30 практично здорових донорів. Результати. До ТЕС вміст у сироватці крові пацієнтів ГП був вищим за показники контролю на 28,80 %; гаптоглобіну — на 20,00; СРП — 82,88; РФМК — 33,60; фібриногену — 60,32; D-димеру — 41,04 %. МНВ виявилося зниженим на 25,40 %, вміст антитромбіну III — на 21,90 %, ФА уповільнена на 63,00 %. Після ТЕС у сироватці крові пацієнтів вміст загальних ГП перевищував показник контрольної групи на 55,80 %, сіалових кислот — на 35,60; сероглікоїдів — 55,26; гаптоглобіну — 61,42; СРП — 151,33 %. Спостерігали додаткове скорочення на 10,58 %, протромбінового часу, АЧТЧ — на 15,40 %, активності антитромбіну III — 19,10 %, підвищення вмісту фібриногену — 34,90; D-димеру — 25,10; РФМК — 36,18; подовження часу ФА — на 29,30 %. Висновки. Для попередження розвитку тромбофілічних станів після ТЕС необхідно проводити моніторинг найбільш інформативних маркерів: підвищення часу ФА, вмісту фібриногену, D-димеру, РФМК, гаптоглобіну. Ключові слова. Ендопротезування, гіперкоагуляція, біохімія, предикція, згортання крові, запалення.

Keywords. Endoprosthesis, hypercoagulation, biochemistry, prediction, blood coagulation, inflammation

Introduction

Deep vein thrombosis (DVT) of the lower extremities is the most serious complication of total knee and hip arthroplasty. It is extremely important to identify the hidden form of DVT, which often develops even before surgical intervention and differs from the clinically manifesting one. The frequency of occult DVT is about 11.9 % after total hip arthroplasty and 20.8 % after total knee arthroplasty [1]. DVT can lead to pulmonary embolism (PE), which is the most severe complication of arthroplasty [2]. Therefore, assessment of changes in coagulation and fibrinolysis indicators is important for predicting DVT in patients scheduled for joint replacement [3].

In the United States, 0.89% of all types of clinically significant venous thromboembolism (VTE), consisting of 0.52 % DVT and 0.43 % PE, were observed after primary total knee arthroplasty. The diagnosis of these cases led to a prolongation of hospital stay by (2.81 ± 0.02) days, an increase in the cost of treatment by (14,212.16 ± 255.64) US dollars, and a 13.04-fold probability of death (CI: 11 08-1535). The presence of comorbidities, namely: cardiac arrhythmias, coagulopathy, water-electrolyte disorders, pulmonary circulation disorders, increased body weight increased the risk of VTE more than 2 times [4].

Almost 50 % of DVT and 40 % of PE within 90 days after total knee arthroplasty can be attributed to the initial health status of patients with osteoarthritis. Complete prevention of venous thromboembolic events after total knee arthroplasty is probably impossible [5].

One of the laboratory criteria useful for registering VTE is an increase in the level of D-dimer in the blood: a sign of acute VTE is threshold values of 2.0–5.9 μg/ml, subclinical — 3.4–5.3 μg/ ml, possibilities of postoperative one — 3.4–5.3 μg/ml [6]. An increase in the content of D-dimer in the blood has been documented in the syndrome of disseminated intravascular coagulation, DVT and PE [7]. For patients over 50 with suspected DVT, the specificity of assessments can be increased by using, instead of the D-dimer threshold value, the value of the adjusted age threshold, which is calculated according to the formula: 5 × age (in units of D-dimer ng/ml DDU) or 10 × age (in alternative units). In a study involving 406 patients aged 50 years or older after total major joint arthroplasty, 39 of whom had asymptomatic DVT, age-adjustment in the assessment of D-dimer concentration in the blood led to an increase in the accuracy of DVT screening [7].

Y. Yang et al. [8] believe that in the prediction of VTE after total knee arthroplasty, determination of the concentration of plasminogen activator inhibitor-1, thrombin-antithrombin complex, and prothrombin fragment F1+2 in the blood is more valuable than the content of D-dimer. The threshold values of these indicators were 35.96 ng/ml, 13.36 ng/mg, 11.1 ng/ml and 2.24 μg/ml, respectively. C. Xue et al. [9] to predict VTE in patients who have undergone total knee arthroplasty, recommend using determination of the blood concentration of thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-antiplasmin complex (PIC), and tissue plasminogen activator-inhibitor complex activator (PAI C). The concentration of TAT, D-dimer and fragment of prothrombin F1+2 to assess the probability of developing hypercoagulation was used by M. Lundbech et al. [10]. At the same time, K. Zhou et al. [11] consider the concentration of thrombomodulin (TM) and tissue plasminogen activator-inhibitor complex (t-PAIK) as independent prognostic indicators of the development of thrombotic complications, and thrombin-antithrombin III and plasmin-α2-plasmin inhibitor complexes as markers for the diagnosis of VTE that has occurred, but not for its prediction.

According to X. Xiong, B. J. Cheng [12], the frequency of hidden DVT in patients even before total knee arthroplasty was 6.85%. The presence of diabetes, chronic kidney disease, coronary heart disease, increased erythrocyte sedimentation rate, blood levels of interleukin-6 and procalcitonin, platelets, thrombocrit and the time from the onset of the disease to admission, a decrease in the content of erythrocytes and blood stasis of the lower extremities before surgery were factors of high risk.

The blood concentration of fibrin monomer (FM), which is formed from fibrinogen by cleavage of two peptides A and two peptides B, reflects prothrombin activity and can be a predictor of thrombotic events earlier than other hemostatic markers. Although the content of D-dimer in the blood has a high sensitivity and prognostic value, its specificity, according to the authors, is lower than FM [7].

The interaction between the inflammation and coagulation systems was revealed, in which inflammation leads to the activation of the coagulation system, and coagulation, in turn, increases inflammatory activity. An increase in the level of inflammatory mediators, in particular, pro-inflammatory cytokines, activates blood coagulation and inhibits physiological anticoagulants. Acceleration of blood coagulation with subsequent generation of thrombin depends on the expression of tissue coagulation factors with

simultaneous suppression of endothelial-related anticoagulation mechanisms, as well as fibrinolytic activity. Activation of protease factors of coagulation also affects specific receptors of inflammatory cells and endothelial cells and triggers an inflammatory reaction [13].

Purpose. Based on the retrospective analysis of biochemical findings in patients with degenerative diseases of large joints before and after total arthroplasty, to determine the changes in the markers of hemostasis system and inflammatory processes, which are the most informative for the preoperative prediction of the development of hypercoagulable conditions.

Material and methods

The study was conducted on the basis of the clinic of the Department of Joint Pathology of the State Establishment Professor M. I. Sytenko Institute of Spine and Joint Pathology of the National Academy of Sciences of Ukraine. The research plan was discussed and approved at the meeting of the Institute's Bioethics Committee (Protocol No. 224 dated 13.06.2023).

Biochemical studies

The study involved retrospective analysis of biochemical findings of 39 patients with degenerative diseases of the hip and knee joints of III–IV stages according to Kellgren-Laurence, who underwent total arthroplasty.

All patients had blood taken from the ulnar vein into a vacuum tube with a citrate anticoagulant to study indicators of the blood coagulation system, as well as into an ordinary vacuum tube to determine biochemical markers of inflammation in blood serum on an empty stomach 1–3 days before surgery and one day after surgery. To obtain plasma, the blood was centrifuged for 15 min at 3000 revolutions/ min. To obtain serum after clot formation, it was separated from serum by centrifugation for 30 min at 1500 revolutions/min. After that, the content in the blood plasma of prothrombin time, international normalized ratio (INR), soluble fibrin monomer complexes (SFMC), D-dimer, fibrinogen, activated partial thrombin time (APT), fibrinolytic activity was determined using sets of ready-made reagents manufactured by the company Granum (Ukraine) [14].

The activity of antithrombin-III in blood plasma was evaluated by the residual activity of thrombin after its interaction with antithrombin- III in defibrinated plasma using reagents of the company Granum (Ukraine) [14].

In blood serum, the content of sialic acids was established by the Hess method, seroglycoids by the Huergo turbidimetric method, haptoglobin by the zrivanol reaction [15], total glycoproteins by the modified method of O.P. Shteinberg and Y. N. Dotsenko [16], C-reactive protein (CRP) semiquantitative latex test according to the instructions for the kit.

According to a similar scheme, samples of venous blood from 30 practically healthy donors, who made up the control group, were examined.

Statistical studies

The obtained results were processed using MS Windows software, license package number 439108-251. The normality of the distribution was checked by the Kolmogorov–Smirnov method. Measurement results are presented as mean square ± standard deviation (M ± m). The Fisher-Student method was used to compare two groups. The difference was considered statistically significant at $p < 0.05$ [17].

Results and their discussion

Before surgical treatment

According to biochemical findings of patients with degenerative diseases of large joints before arthroplasty, a significant activation of inflammatory processes was revealed compared to the control group. Their serum content of total glycoproteins (GP) was higher by 28.80 %, haptoglobin by 20.00 %, SRP by 82.88 %, SFMC by 33.60 % (Table). Under these circumstances, a tendency to hypercoagulation was observed: INR was inferior to this in the control group by 25.40 %. A significant increase in the content of fibrinogen in the blood of patients was also recorded, which amounted to an average of 60.32 % at the time of the study. This indicator usually increases in response to the development of the inflammatory process in the human body.

At the same time, the manifestation of such a marker of thrombotic readiness or thrombosis as blood content of D-dimer, which was increased by 41.04 % in the examined patients, was determined (Table).

These deviations were particularly dangerous in combination with an increase in the duration of fibrinolytic activity. Acceleration of blood clot lysis can partially balance the body's homeostasis under conditions of excessive activation of the coagulation system. But in the examined patients, fibrinolytic activity slowed down by 63.00 %, which, together with the obtained indicators of activation of coagulation factors, led to an increase in the risk of developing thrombotic complications even before surgical treatment. The content of antithrombin III, which is a sign of the development of thrombophilia, was also reduced by 21.90 %.

The obtained results indicate that before the operation, the patients had moderate signs of the risk

of developing thrombotic complications. However, under the conditions of massive tissue damage during total endoprosthesis, the specified deviations can deepen and will almost always trigger the development of conditions that will require intensive medical correction or risk to life.

After surgical treatment

After the operation, it is predicted that a significant increase in the activity of the inflammatory background and the manifestation of markers of inflammatory processes will be observed. In particular, the content in blood serum of total GPs exceeded the indicator of the control group by 55.80%, sialic acids by 35.60%, seroglycoids by 55.26%, haptoglobin by 61.42%, CRP by 151.33% (Table).

This could not but change the course of other metabolic processes: activation of the blood coagulation system was determined, while the prothrombin time was 20.70 % shorter than in the control group. One of the markers of the inflammatory process is the content

Table

Biochemical indicators of patients with degenerative diseases of large joints before total endoprosthetic surgery and one day after it

Indicator	Control group, n = 30	Examination term	
		Before operation, n = 39	Day after operation, n = 39
Prothrombin time, s	14.40 ± 0.34	12.76 ± 0.35 –11.39 % [1), 3)]	11.41 ± 0,.41 –20.70 % [1), 6)] –10.58 % [2), 4)]
International normalized ratio	1.14 ± 0.07	0.85 ± 0.06 –25.40 % [1), 4)]	0.73 ± 0.05 –35.90 % [1), 5)] –14.10 % [2), 3)]
Activated partial thrombin time, s	29.50 ± 5.00	26.43 ± 0.65 –10.40 % [1), 3)]	22.36 ± 0.63 –24.20 % [1), 6)] –15.40 % [2), 6)]
Fibrinogen content, g/l	2.52 ± 0.12	4.04 ± 0.26 +60.32 % [1), 6)]	5.45 ± 0.29 +116.27 % [1), 6)] +34.90 % [2), 6)]
Fibrinolytic activity, min	6.53 ± 0.34	10.65 ± 0.48 +63.00 % [1), 6)]	13.78 ± 0.53 +111.00 % [1), 6)] +29.30 % [2), 6)]
Content of soluble fibrin-monomeric complexes, mg/100 g	3.33 ± 0.05	4.45 ± 0.38 +33.60 % [1), 4)]	6.06 ± 0.57 +81.90 % [1), 6)] +36.18 % [2), 4)]
D-dimer content, ng/ml DDU	180.14 ± 11.25	254.06 ± 17.13 +41.04 % [1), 5)]	318.04 ± 19.36 +76.55 % [1), 6)] +25.10 % [2), 4)]
Content of antithrombin-III, %	95.40 ± 2.60	74.50 ± 3.50 –21.90 % [1), 4)]	60.30 ± 2.90 –36.80 % [1)] –19.10 % [2), 6)]
Content of total glycoproteins, g/l	0.680 ± 0.008	0.877 ± 0.022 +28.80 % [1), 4)]	1.061 ± 0.026 +55.80 % [1), 6)] +21.11 % [2), 6)]
Content of sialic acids, mmol/l	1.91 ± 0.17	2.13 ± 0.13 +11.52 % [1), 4)]	2.59 ± 0.15 +35.60 % [1), 6)] +21.60 % [2), 3)]
Content of seroglycoids, g/l	0.38 ± 0.06	0.43 ± 0.03 +13.15 % [1), 3)]	0.59 ± 0.06 +55.26 % [1), 6)] +37.20 % [2), 4)]
Content of haptoglobin, g/l	0.70 ± 0.02	0.84 ± 0.09 +20.00 % [1), 4)]	1.13 ± 0.08 +61.42 % [1), 5)] +34.52 % [2), 4)]
Content of C-reactive protein, mg/l	4.50 ± 0.62	8.23 ± 0.69 +82.88 % [1), 6)]	11.31 ± 0.96 +151.33 % [1), 6)] +37.42 % [2), 5)]

Notes: [1)] — difference compared to the indicators of individuals of the control group; [2)] — difference compared to the indicators of the patients before the operation; [3)] — $p > 0.05$; [4)] — $p < 0.05$; [5)] — $p < 0.01$; [6)] — $p < 0.001$

of fibrinogen, which moved towards hypercoagulation — increased by 116.27%. APT decreased by 24.20 %, indicating the activation of the internal blood coagulation mechanism. The anticoagulation system also underwent significant changes. The duration of clot lysis (fibrinolytic activity) increased by 111.00 %, which is a sign of imbalanced regulation of the coagulation and anticoagulation system, its transition to another level, more dangerous for the patient, with a tendency to develop hypercoagulable conditions. A sign of the presence of microthrombi and their resorption is an increase in D-dimer content by 76.55 %, as well as SFMC by 81.90 % compared to the control.

It was diagnosed that as a result of the operation, the indicators of the inflammatory process in the patient's body increased sharply: the content of total glycoproteins by 21.11 %, sialic acids by 21.60 %, seroglycoides by 37.20 %, haptoglobin by 34.52 % and CRP by 40.00 %.

At the same time, direct signs of more severe hypercoagulation were recorded: 10.58% less than before the operation, prothrombin time value, APT by 15.40 %. Fibrinogen concentration after surgery increased by 34.90 %. The activity of antithrombin III decreased by 19.10 % compared to the indicator before surgical intervention and by 36.80 % compared to the value in the control group. Signs of microthrombi were observed, which is evidenced by an excess of the preoperative level by 25.10 % of the concentration in the blood of D-dimers and by 36.18 % — SFMC.

Development of a hypercoagulable state after surgery was aggravated by the prolongation of fibrinolytic activity by 29.30 % (Table).

Discussion

In general, a comparison of the results of the biochemical examination of patients with degenerative diseases of large joints before and after total arthroplasty with the indicators of the control group (practically healthy people) showed significant deviations even before the operation. In fact, the state of hypercoagulability was quite noticeable, which coincides with the information of other researchers, who found the development of asymptomatic deep vein thrombosis in 39 of 406 patients with osteoarthritis of the large joints before total arthroplasty of the large joints. The authors noted correlations with age (odds ratio (OR) = 1.067; p = 0.003) and the blood level of D-dimer (OR = 1.331; p = 0.025) [1].

We can assume that the mentioned changes occurred because the activity of inflammatory processes was significantly increased in the body of the patients, and active inflammation through the system of general protective reactions, which is reflected, in particular, by an increase in the content of fibrinogen, activated the blood coagulation system. According to literature sources, fibrinogen acts as an acute phase protein in patients who underwent total arthroplasty of large joints [18].

Major orthopedic intervention (total arthroplasty of large joints) always results in temporary activation of inflammation as a protective factor. Presumably, the inflammatory reaction is intensified due to operative stress, which is reflected by an increase in the level of cortisol 24 hours after it [19]. Since inflammation and the endocrine system are cross-linked and bidirectional, it is logical to expect activation of both systems after an intervention. According to A. Prete et al. [20] the cortisol level rises rapidly after surgery and normalizes within 24–48 hours. In patients with degenerative diseases of large joints, this was superimposed on the already activated coagulation system, which led to an excessive increase in the manifestations of its functioning and an increase in the risks of hypercoagulable complications. In particular, H. Bawa et al. [21] noted that patients with a preoperative diagnosis of hypercoagulation had a higher risk of postoperative DVT, which generally occurs quite often after total arthroplasty of large joints. Thus, out of 750 patients with gonarthrosis and subsequent total arthroplasty of large joints, according to the results of ultrasound dopplerography of the deep veins of both lower extremities on the 3rd day after surgery, DVT was diagnosed in 176 patients, its absence in 574 [22].

It can be assumed with a high degree of probability that only significant antithrombotic therapy kept the examined patients after total arthroplasty of large joints from the massive development of thrombotic conditions. At the same time, the increase in coagulation activity is not the same in different individuals, and typical preventive and curative therapy can trigger bleeding and thrombotic complications.

Conclusions

Biochemical indicators of blood of patients with osteoarthritis of large joints, who subsequently underwent total arthroplasty, were characterized by markers of the inflammatory process, as well as an increase in indicators of the blood coagulation system against the background of inhibition of fibrinolysis, indicating the thrombophilic readiness of the patient group even before surgery.

Total arthroplasty of large joints led to a further increase in the level of markers of the blood coagulation system, signs of suppression of fibrinolytic activity along with the activation of inflammatory processes.

A close relationship between the severity of inflammatory processes and the development of thrombophilia in examined patients who underwent total arthroplasty of large joints was revealed.

According to the results of a retrospective analysis of blood coagulation/anticoagulation indicators and markers of inflammation, the most informative in terms of predicting the development of thrombophilic conditions before surgery are indicators of an increase in the content of C-reactive protein in the blood by 82.88 %, the duration of fibrinolytic activity (by 63.00 %), the content fibrinogen (by 60.32 %), D-dimer (by 41.04 %), soluble fibrin-monomeric complexes (by 33.60 %), total glycoproteins (by 28.88 %) and haptoglobin (by 20.00 %)), as well as a reduction in the international normalized ratio by 25.40 % and the content of antithrombin III in the blood by 21.90 %.

In order to prevent the development of hypercoagulable states after total arthroplasty of large joints, it is necessary to monitor significant indicators of the coagulation system, as well as markers of the inflammatory process.

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

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CHANGES IN INDICATORS OF THE COAGULATION SYSTEM AND MARKERS OF INFLAMMATION IN THE BLOOD OF PATIENTS WITH DEGENERATIVE DISEASES OF LARGE JOINTS IN THE CASE OF TOTAL ARTHROPLASTY

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