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Research Article

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Acute Thrombosis of Lower Extremities Veins in Surgical Patients With COVID-19

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AIM OF THE STUDY To establish the incidence of acute thrombosis of the veins of the lower extremities and the activity of the most significant trigger agents that led to this complication in patients with a new coronavirus infection.

MATERIAL AND METHODS The clinical section of the work is presented by observations of 123 patients with acute surgical pathology and thrombosis of the veins of the lower extremities. The first group (comparison) (n=48) included patients with thrombosis of the veins of the lower extremities, the second (studied) group (n=87) included patients with a similar problem that arose against the background of coronavirus infection. All patients underwent surgical interventions: thrombectomy and plication. Before surgery, on the 1st, 4th and 7th days after surgery, disorders of the hemostasis system, the severity of endogenous intoxication syndrome, and lipid metabolism were assessed.

RESULTS Damage to the veins of the lower extremities in patients with acute surgical pathology and new coronavirus infection occurs much more often, in 8.04% of cases, than in such patients without COVID-19, in 0.76% (χ^2=252.5, p<0.001). Of the 87 patients with acute venous thrombosis of the inferior vena cava system and COVID-19, 63 patients (72.41%) were operated on. In the early postoperative period, venous rethmbosis occurred in 11 (17.5%) patients. The mortality rate was 6.3%. According to thromboelastography, in the main group the values of such parameters as reactive time, the growth rate of the fibrin network and its structure formation and the maximum strength of the clot were statistically significantly higher than in the control group, which indicates the predominance of hypercoagulation in these patients. Patients in this group showed more significant phenomena of endotoxemia, oxidative stress and activation of phospholipases.

CONCLUSION With a new coronavirus infection, surgical patients have a high probability of developing threatening thrombohemorrhagic complications. The most important trigger for their occurrence is significant disturbances in the hemostatic system, which are generally characterized by an increased ability of the blood to form thrombosis against the background of a decrease in its fibrinolytic activity. Disturbances in the hemostatic system occurred against the background of oxidative stress, activation of phospholipases and endotoxemia. The obtained material is proof of the significance of the new coronavirus COVID-19 infection worsens coagulopathy, which plays an important role in the pathogenesis of the disease in general and the development of complications.

Keywords: coronavirus infection, venous thrombosis, coagulopathy, endotoxemia, oxidative stress

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A – the current amplitude
ABR – albumin binding reserve
CI – coagulation index
CT – computed tomography
DC – diene conjugates
EAC – effective albumin concentration
G – maximum clot strength
IT – toxicity index
K – time of clot formation
MA – maximum amplitude
MDA – malondialdehyde
R – reactive time
TAC – total albumin concentration
TEG – thromboelastography

INTRODUCTION

Currently, the fight against the incidence of new coronavirus infection (COVID-19) and its consequences is the most pressing issue among medical specialists [1]. To date, scientists have repeatedly proven that the *SARS-CoV-2* virus and its strains affect not only the alveolar tissue, but also, sometimes to an even greater extent, the endothelial cells of the vascular walls, which leads to systemic microcirculatory dysfunction and disruption of the rheological properties of the blood [2, 3]. The main factor inducing these disorders is the hyperfunction of the blood coagulation system with the formation of an excessive amount of procoagulants, stimulating the development of disseminated intravascular coagulation syndrome with generalized microthrombosis [4-6]. In addition, endothelial disorders lead to an increase in membrane-destructive processes with increased activity of lipid peroxidation and hyperproduction of reactive oxygen species, which causes an imbalance in the system of natural pro- and antioxidants [7, 8]. Taking into account the above, it is logical to assume

that with COVID-19 the basis is created for the formation of various complications of a thrombohemorrhagic nature. The problem is especially acute in patients who have undergone surgical interventions.

The aim of the work: to establish the frequency of acute thrombosis of the veins of the lower extremities and the activity of the most significant trigger agents that led to this complication in surgical patients with COVID-19.

MATERIAL AND RESEARCH METHODS

The work is based on the materials obtained in the S.V. Katkov Republican Clinical Hospital (Saransk), which since 2020 has been serving as a hospital for patients with COVID-19. During the period 2020–2021, 1,082 patients were treated in the surgical department, of which 87 patients (8.04%) developed lower extremity vein thrombosis. These patients were the object of the study (main group, group II). During the period 2012–2019, 6,348 patients were treated in the surgical department, of which 48 patients (0.76%) (comparison group, group I) had similar lower extremity vein lesions, but they did not have *COVID* -19 lesions.

The diagnosis of coronavirus infection was established based on clinical, laboratory and instrumental data. According to the results of computed tomography (CT), lung damage in 34 patients (39.1%) was up to 25% (CT1), in 39 patients (44.8%) from 35 to 50% (CT2), in 14 patients (16.1%) more than 50% (CT3).

Patients received complex treatment for the underlying pathology and coronavirus infection. The volume and nature of therapy was determined according to temporary methodological recommendations and included etiotropic, pathogenetic and symptomatic components.

The patients in the groups matched in terms of the main gender and age characteristics, venous lesions, and the volume and nature of the surgical intervention ($\chi^2 = 1.832 \div 2.585$, $p = 0.594 \div 0.767$). In the first group, the age of patients was 57.1 ± 5.2 years, and in the second group it was 53.3 ± 4.7 years. There were 22 men (45.8%) and 26 women (54.2%) in the first group, and 49 (56.3%) and 38 (43.7%) in the second, respectively.

The diagnosis of acute thrombosis in the inferior vena cava system was based on clinical and instrumental data: signs of the presence of a thrombus and blood flow disturbances were recorded during angioscanning during ultrasound Dopplerography.

The level of thrombus detection in patients of the first group: veins of the lower leg, 21 (43.8%), superficial femoral vein, 15 (31.3%); popliteal vein, 12 (25.0%); the second: 33 (37.9%), 30 (34.5%) and 21 (24.1%), respectively.

Patients in both groups underwent the same type of surgical interventions to restore the patency of a certain segment of the deep venous bed by removing floating thrombotic masses and creating an obstacle to prevent the migration of thrombi into the pulmonary artery (vein plication).

Examination stages: before surgery, 1st, 4th and 7th days after surgery. In addition to routine studies, patients underwent a number of special examinations. The state of the hemostasis system was established based on thromboelastography (TEG) on *a TEG*® 5000 *Thrombelastograph*® (USA), the severity of endogenous intoxication syndrome was assessed based on the content of toxic products of hydrophilic (by the level of average-weight molecules) and hydrophobic (by total (TAC) and effective albumin concentration (EAC), the albumin binding reserve (ABR) was calculated (TAR = ECA/TAC and the toxicity index (TI); TI = TAC/ECA–1), the intensity of oxidative stress was based on the content of primary and secondary molecular products of lipid peroxidation, and phospholipase activity was based on the activity of phospholipase A_2.

When decoding the TEG, the following parameters were considered: *R* (reactive time) determines the blood clotting period and characterizes the 1-2nd phase of clotting; *K* (clot formation time) is coagulation time, reflecting its kinetics of increasing clot strength, characterizes the 3rd phase of blood clotting; α-angle (clot strength value) reflects the growth rate of the fibrin network and its structure formation and characterizes the level of fibrinogen in the plasma; *G* (maximum clot strength) is clot strength as an elastic modulus; *CI* (coagulation index) is a derivative parameter from *R*, *K*, MA (maximum amplitude) and the angle α, characterizes the coagulation potential of the patient's blood as a whole; MA characterizes the maximum dynamic properties of the connection of fibrin and platelets through GP *II* b / III *a* and reflects the maximum clot strength; A (current amplitude) is the amplitude of the thromboelastogram at the last moment of time during the current measurement.

Statistical processing of the obtained results was performed using *the Statistica* 6.0 *for Windows software package* with calculation of the Student's criterion (*t*) and χ^2, the arithmetic mean of the sample population (*M*), and the arithmetic mean error (*m*). To check the samples for normal distribution, the Kolmogorov–Smirnov criterion with Lilliefors correction was used. Differences between indicators were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

As indicated above, lower extremity vein damage in patients with acute surgical pathology and COVID-19 occurs significantly more often, 8.04%, than in such patients without *COVID*-19, 0.76% ($\chi^2 = 252.5$, $p < 0.001$). In 4 patients of this group (0.37%) pulmonary embolism developed.

Of 87 patients with acute thrombosis of the veins of the inferior vena cava and IVC system, 63 patients (72.4%) were operated on. In the early postoperative period, 11 (17.5%) developed venous rethrombosis. The mortality rate was 6.3% (4 patients).

Thus, in patients operated on for various acute surgical diseases and having *COVID*-19, acute thrombosis of the veins of the lower extremities occurs much more often. One of the objectives of the work is to determine the causes of the established. In this regard, there is certainly a need, first of all, to study the state of the hemostasis system and a number of pathological processes on which its state largely depends.

According to TEG data, in group II, the reactive time (*R*) before surgery, as well as on the 1st, 4th and 7th days after, was statistically significantly lower than the reference values by 21.1, 27.1, 20.1 and 15.7% ($p < 0.05$), respectively, which reflects the protracted nature of disorders in the hemostasis system (Table 1). More pronounced positive dynamics were noted in the comparison group: before surgery, on the 1st and 4th days of observation, *R* was statistically significantly lower than the reference values by 9.9, 12.1 and 7.5% ($p < 0.05$), respectively, normalizing by the 7th day of observation. It is worth noting that *R* in group II at all stages of observation was statistically significantly lower than the values of group I by 12.4 – 17.1% ($p < 0.05$).

Table 1

Parameters of thromboelastography of patients (M±m)

Indicator	Group	Norm	Stage of the observation period (day)			
			Before surgery	1	4	7
R, min	I	4.13±0.12	3.72±0.14*	3.63±0.13*	3.82±0.15*	4.08±0.14
	II		**3.26±0.15***	**3.01±0.11***	**3.30±0.15***	**3.48±0.16***
K, min	I	1.84±0.11	2.09±0.13	2.18±0.13*	2.07±0.14	1.89±0.12
	II		2.12±0.15	2.26±0.17*	2.17±0.17	2.03±0.18
α – angle, degrees	I	62.1±1.95	56.2±2.04*	50.1±2.19*	56.3±2.09*	60.1±2.33
	II		**49.1±2.11***	**45.7±2.14***	**48.8±2.31***	**54.4±2.17***
MA, %	I	61.9±1.85	56.3±1.44*	53.6±1.81*	58.9±1.57	60.6±1.83
	II		53.2±1.57*	50.2±1.48*	**52.4±1.43***	**56.0±1.72***
G, d/sc	I	7.21±0.21	6.48±0.31*	6.24±0.27*	6.58±0.20*	6.88±0.25
	II		6.13±0.23*	6.04±0.23*	**6.01±0.18***	**6.28±0.22***
A, mm	I	50.8±1.66	57.1±2.16*	59.3±2.41*	56.7±2.13*	53.7±2.30
	II		**63.9±2.36***	**66.1±2.45***	**64.4±2.57***	**60.6±2.44***
CI, %	I	0.85±0.07	0.97±0.06	1.12±0.08*	0.96±0.07	0.91±0.06
	II		1.05±0.07*	1.17±0.11*	**1.16±0.08***	**1.12±0.07***

Notes: * – statistically significant difference from reference values (p<0.05); bold font – statistically significant difference from the indicators of group I (p<0.05).
A – the current amplitude; MA - maximum amplitude; CI – coagulation index; G – the maximum strength of the clot; K – the time of clot formation; R - reactive time

A similar picture was observed with the α– angle and *G index*: statistically significant differences in the indices from the normal values in group I were revealed before the operation, on the 1st and 4th days of observation: a decrease in the α– angle indices by 9.5, 19.3, 9.3% (p <0.05), *G* — by 10.1, 13.5, 8.7% (p <0.05), respectively, subsequently approaching normal values. In group II, the deviations of α– angle and *G index* before the operation, on the 1st, 4th and 7th days of observation were statistically significantly lower than the reference values by 20.9 and 15.0, 26.4 and 16.2, 21.4 and 16.6, 12.4 and 12.9% (p <0.05), respectively. In addition, the α -angle index in Group II at all stages of observation was lower than the values of Group I by 8.8–13.3% (p *<0.05). The values of the G* index were statistically significantly different only by the end of observation: on the 4th and 7th days of observation, the *G index* in Group II was reduced relative to Group I by 8.7% (p <0.05).

The time of clot formation in both groups was similar, statistically significantly differing from the reference values only on the 1st day after surgery: the *K indicator* was increased in groups I and II by 18.5 and 22.8% (p <0.05), respectively.

The MA parameter was lowered in patients of group II relative to normal values both before surgery and on the 1st, 4th, 7th day of postoperative observation by 14.1, 18.9, 15.3, 9.5% (p < 0.05), respectively, while in group I this indicator was statistically significantly lower than normal only before surgery and on the 1st day of observation by 9.0 and 13.4% (p < 0.05), respectively, and returned to reference values by the 4th day after surgery, which was statistically significantly higher than similar values of this indicator in group II by 7.6–11.0% (p < 0.05).

When determining the current amplitude parameter, it was found that this parameter in group II was statistically significantly higher than the reference values before the operation and on the 1st, 4th, 7th day of observation by 25.8, 30.1, 26.8, 19.3% (p <0.05), respectively, while in group I a statistically significant increase in this indicator was observed before the operation, on the 1st and 4th day of observation by 12.4, 16.7, 11.6% (p <0.05), respectively, returning to the normal level by the 7th day. Note that throughout the observation period, the values of the current amplitude indicator in group II statistically significantly exceeded similar values in group I by 11.5–13.6% (p <0.05). The coagulation index values in group II were statistically significantly higher than the normal values before surgery, on the 1st, 4th, 7th day of observation by 23.5, 37.6, 36.5, 31.8% (p <0.05), respectively, whereas in group I a statistically significant increase in this indicator was recorded only on the 1st day after surgery by 31.8% (p <0.05) with a rapid tendency to normalization. At the same time, the CI values in group I statistically significantly exceeded similar values in group II on the 4th and 7th day of observation by 20.8 and 23.1% (p <0.05), respectively. Undoubtedly, the indicated homeostasis disorders at the body level created a sufficiently unfavorable background for the functioning of all systems and could not but affect the severity of the postoperative period, in particular, the development of complications.

According to the obtained data, the endotoxicosis indices in the studied groups of patients did not return to normal values by the final observation period after surgery, but the most pronounced deviations in relation to similar data in the comparison group were noted in patients with concomitant COVID-19 . Thus, the level of medium-weight molecules detected at a wavelength (λ) of 280 nm and 254 nm before surgery, on the 1st, 4th, 7th day of the postoperative period in Group II were statistically significantly higher than the reference values by 49.6 and 46.9, 69.4 and 57.9, 62.0 and 50.4, 42.1 and 38.9% (p <0.05), respectively, which reflects a slowly ongoing recovery process. In Group I, these indicators also exceeded normal values at all stages of observation by 24.8–47.9 and 21.4–35.9% (p <0.05), but the positive dynamics of these indicators was more pronounced: the level of medium-weight molecules at λ =280 nm and λ =254 nm in Group I at all stages of observation was lower than similar indicators in Group II by 13.9–18.4 and 14.4–18.7% (p <0.05), respectively (Table 2).

Table 2

Indicators of endotoxemia in patients

Indicator	Group	Norm	Observation period duration (days)			
			Before surgery	1st	4th	7th
Medium-mass molecules (λ =280 nm), conventional units	I	0.242±0.015	0.317±0.017*	0.358±0.017*	0.331±0.017*	0.302±0.017*
	II		**0.362±0.016***	**0.410±0.020***	**0.392±0.021***	**0.344±0.018***
Medium-mass molecules (λ =254 nm), conventional units	I	0.337±0.017	0.417±0.018*	0.458±0.019*	0.433±0.018*	0.409±0.019*
	II		**0.495±0.020***	**0.532±0.021***	**0.507±0.022***	**0.468±0.022***
Effective albumin concentration, g/l	I	46.08±1.11	34.15±1.20*	30.12±1.22*	32.15±1.19*	38.14±1.33
	II		**30.17±1.08***	**22.56±1.28***	**27.22±1.05***	**32.07±1.04***
Albumin binding reserve, conventional units	I	0.897±0.029	0.742±0.026*	0.704±0.028*	0.729±0.021*	0.787±0.025*
	II		**0.683±0.020***	**0.642±0.025***	**0.677±0.024***	**0.704±0.027***
Toxicity index, conventional units	I	0.111±0.009	0.278±0.016*	0.313±0.024*	0.283±0.020*	0.221±0.014*
	II		**0.385±0.020***	**0.409±0.028***	**0.367±0.025***	**0.308±0.018***

Notes: * — statistically significant difference from reference values (p<0.05); bold font — statistically significant difference from the indicators of group I (p<0.05)

A delay in the return of endogenous intoxication indices to reference values was noted in the values of effective albumin concentration, the level of which before surgery, on the 1st, 4th, 7th day of the postoperative period in group II patients was statistically significantly lower than normal by 34.5, 51.0, 40.9, 30.4% (p <0.05), respectively, whereas in group I differences from the norm were recorded only before surgery, on the 1st and 4th day of observation and were lower than normal values by 25.9, 34.6, 30.2% (p <0.05), respectively, recovering by the end of the observation period.

A similar picture was observed in terms of the values of albumin reserve binding capacity: before surgery and at the stages of the postoperative period in groups I and II of patients, this indicator was statistically significantly lower than the norm by 17.3 and 23.9, 21.5 and 28.4, 18.7 and 24.5, 12.3 and 21.5% (p < 0.05), respectively. It is worth noting that at all stages of observation, the effective concentration and reserve binding capacity of albumin in group II were lower than those in group I by 11.7–25.1 and 7.1–10.5% (p < 0.05), respectively.

The toxicity index in dynamics in Group I was higher than the norm throughout the entire observation period by 150.5, 182.0, 155.0 and 99.1% (p <0.05), respectively, while in Group II these deviations in similar observation periods differed from those in the comparison group by 29.7–39.4% (p <0.05), exceeding the reference values by 256.8, 268.5, 230.6 and 177.5% (p<0.05), respectively (statistically significant in all 3 cases).

These data indicate complications in the adaptation of the body's detoxification systems when COVID-19 is added.

As we know, one of the factors that complicates the rapid restoration of the structural and functional state of tissue and organ structures in acute surgical pathology is membrane destabilization, which occurs as a result of increased lipid peroxidation and phospholipase activity.

Biochemical studies of blood plasma in the studied groups of patients showed a significant increase in the levels of diene conjugates (DC) and malondialdehyde (MDA) in blood plasma, especially

in the group of patients with COVID-19 (Table 3). Before the operation, on the 1st, 4th and 7th days of postoperative observation, the level of DC and MDA in group I was 70.0 and 42.4, 90.0 and 52.4, 85.0 and 47.2, 55.0 and 30.7% (p <0.05), respectively, higher than normal values, while in group II similar values were 125.0 and 63.2, 155.0 and 77.5, 130.0 and 68.8, 95.0 and 58.4% (p <0.05), respectively, higher than normal, which in comparison with group I was higher by 24.3–34.2 and 14.6–21.2% (p <0.05), respectively (statistically significant in all 3 cases). Thus, if in the comparison group by the 7th day of postoperative observation there was a pronounced positive dynamics in the level of the considered peroxidation products, then in the group of patients with COVID-19 a protracted nature of the studied dysfunctions was noted.

At the same time, the enzymatic antioxidant potential in the group of patients with coronavirus infection fell more significantly, as evidenced by a more pronounced decrease in superoxide dismutase activity relative to the physiological norm. Thus, at all stages of observation, the level of superoxide dismutase in group II was 27.7, 33.3, 30.4, and 24.2% (p <0.05), respectively, below the norm, while in group I this indicator was 17.0, 25.4, 17.5% (p <0.05), normalizing by the 7th day of observation. It should be noted that in group II, compared with group I, superoxide dismutase activity was lower at all stages of observation by 10.6–20.7% (p <0.05) (statistically significant in all 3 cases). We also emphasize that in the group of patients with added COVID-19, phospholipase A_2 activity significantly increased and was restored for a long time . Before the operation and at the stages of the postoperative period, the level of phospholipase A_2 in group II was statistically significantly higher than normal values by 386.8, 470.6, 352.9 and 307.4% (p <0.05), respectively, and higher than similar indicators in group I by 270.6, 305.9, 188.2 and 83.8% (p <0.05), respectively.

CONCLUSION

The obtained material gives grounds to assert that with the new coronavirus infection in surgical patients the probability of developing threatening thrombohemorrhagic complications increases significantly (more than 10 times). Undoubtedly, and this is confirmed by our studies, and the most important trigger for their occurrence are significant disturbances in the hemostasis system, which are generally characterized by an increased ability of blood to form thrombi against the background of a decrease in its fibrinolytic activity. Of undoubted scientific and practical interest is a fragment of the work that determines the possible mechanisms of transformation of the hemostasis system. In this series, first of all, it is necessary to note the phenomena of oxidative stress and activation of phospholipases, which, as is known, modulate the phospholipid bilayer of membranes of various cells, including outside the bloodstream, activating the hemostasis system in the direction of thrombus formation. We also note the role of endogenous intoxication in this pathological process. On the one

Table 3

Dynamics of indicators of lipid peroxidation and the antioxidant system in the blood plasma of patients

Indicator	Group	Norm	Stage of the observation period (day)			
			Before surgery	1	4	7
Level of DC, conventional units/mg lipids	I	0.20±0.013	0.34±0.017*	0.38±0.019*	0.37±0.018*	0.31±0.019*
	II		0.45±0.020*	0.51±0.023*	0.46±0.024*	0.39±0.021*
MDA level, nmol/g protein	I	2.31±0.16	3.29±0.15*	3.52±0.19*	3.40±0.17*	3.02±0.17*
	II		3.77±0.17*	4.10±0.22*	3.90±0.19*	3.66±0.20*
Superoxide dismutase activity, conventional units/mg protein	I	4.05±0.19	3.36±0.13*	3.02±0.15*	3.34±0.16*	3.87±0.14
	II		2.93±0.16*	2.70±0.18*	2.82±0.17*	3.07±0.20*
$_{A2}$ activity, μmol/s/g protein	I	0.068±0.008	0.252±0.016*	0.276±0.018*	0.196±0.019*	0.125±0.014*
	II		0.331±0.024*	0.388±0.025*	0.308±0.027*	0.277±0.024*

Notes: * — statistically significant difference from reference values (p<0.05); bold font — statistically significant difference from the indicators of group I (p<0.05).
DC – conjugated dienes; MDA – malonic dialdehyde

hand, the hemostasis system is also modulated in toxemia, on the other hand, a significant level of toxic products in the blood indicates a possible lesion of one of the most important organs of detoxification – the liver, which is known to be the most important in the production of blood coagulation factors. It should also be noted that even against the background of complex therapy in the early postoperative period, homeostasis disorders persist, indicating a protracted nature of the pathological process and a high probability of its progression, and was expressed in recurrent thrombus formation, including fatal ones (mortality rate 6.3%).

1. Thrombosis of the veins of the lower extremities in patients with acute surgical pathology and new coronavirus infection occurs in 8.04%, and in 0.76% (χ^2 = 252.5, p <0.001) without this type of comorbid pathology.

2. Damage to the veins of the lower extremities in *COVID*-19 occurs against the background of activation of the coagulation system and suppression of the fibrinolytic capacity of the blood: the reactive time indicator in the early postoperative period is 12.4–17.1% less than that in the comparison group (p <0.05); the value of the coagulation index – more on the 4th and 7th days by 20.8 and 23.1% (p <0.05), respectively.

3. A significant modification of the hemocoagulation state in the new coronavirus infection is associated with endotoxinemia (an increase in the level of water-soluble toxins compared to the comparison group by 13.9–18.7%, water-insoluble toxins by 29.7–39.4% (p <0.05)), oxidative stress (the level of molecular products of lipid peroxidation increased by 14.6–34.2% (p <0.05)) and activation of phospholipase A_2 (by 83.8–305.9% (p <0.05)).

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