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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

ROLE OF THROMBODYNAMICS GLOBAL COAGULATION TEST IN IMPROVING TREATMENT RESULTS IN PATIENTS WITH CORONAVIRUS INFECTION AT A COVID-19 HOSPITAL

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In December 2019, a new coronavirus (SARS-CoV-2) caused an outbreak of a potentially dangerous infection [1], defined by the World Health Organization (WHO) as – COVID-19 ("Coronavirus disease 2019"). The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy), in 3-4% of patients the development of acute respiratory distress syndrome (ARDS) was registered. Hypercoagulative syndrome with thrombosis and thromboembolism is developed in a significant proportion of patients, other organs and systems also are affected (central nervous system, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop [2].

Gradual increasing inflammation in patients leads to an overstraining of their immune system, a sharp increase in the production of cytokines that stimulate the development of infiltrative fibrosis, exudative damage to lung tissue, desquamation of lung epithelial cells with loss of alveolar airiness [3]. This condition is more like the development of alveolitis than true pneumonia, the alveoli "sink", and the lungs lose their ability to exchange gas. The lung tissue becomes airless, with expressed edema and areas of atelectasis [4].

SARS-CoV-2 uses the angiotensin converting enzyme receptor 2 (ACE2) which expresses at high levels in the lungs, kidneys, gastrointestinal tract, liver, vascular endothelial and arterial smooth muscle cells. COVID-19 is a multisystem inflammatory syndrome, as all these organs and systems are potential targets for SARS-CoV-2 infection [5-7]. Therefore successful treatment of COVID-19 is possible only with the use of combination therapy, including the use of typical multi-purpose drugs. Taking into account that COVID-19 is a serious threat for worldwide, it is necessary to find new effective schemes for its prevention and treatment.

Another feature of coronavirus infection is an significant prothrombotic (procoagulative) status, accompanied by a large number of thrombotic events, especially venous thromboembolic complications (VTEC) [8,9]. Later, this phenomenon was named "COVID-19-associated coagulopathy". [10].

It is assumed that various mechanisms underlie prothrombotic changes in COVID-19. These are disseminated intravascular coagulation (DIC), pulmonary intravascular coagulopathy (PIC) or microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS), secondary hemophagocytic lymphohistiocytosis, thrombotic microangiopathy (TMA), and endotheliitis [11,12].

Coagulopathy with a predominance of the hypercoagulative phase of DIC-syndrome is a key link in the development and advance of COVID-19-associated pneumonia. Disseminated intravascular coagulation syndrome accompanies clinical advance from systemic inflammation response syndrome to severe sepsis and septic shock. In turn, the advance of DIC leads to multiple organ failure, which is associated with high mortality rates [13].

The main laboratory markers of coagulopathy are D-dimer level, prothrombin time (PT), number of thrombocytes, and changes in fibrinogen concentration. The concentration of D-dimer in the blood is an important biomarker for predicting the severity of coronavirus infection in patients with COVID-19, which is important for suspected thromboembolism. There is evidence that if a patient with COVID-19 has a high level of D-dimer on admission to the hospital, the risk of death increases [14]. According to the results of a number of studies, patients with COVID-19 had a worse prognosis if they showed signs of hypercoagulation (prolonged PT, APTT, increased levels of D-dimer and other fibrin breakdown products, while the antithrombin activity was lower than the reference values) [15,16]. The D-dimer is commonly used to confirm or eliminate thrombotic processes, such as deep vein thrombosis or pulmonary embolism [17].

However, local coagulation tests can only assess the activity of individual parts of the hemostatic system and detect a significant deficiency of factors (over 40%), but they have low sensitivity and are not able to give information about the general hemostatic state of the blood. Global coagulation tests (thrombin production test, thromboelastogram, thrombodynamics test) provide an integral picture of the changes in the coagulation system, taking into account all possible factors of influence.

The aim of the study was to evaluate the effectiveness of the global coagulation thrombodynamics test for monitoring and correcting the hemostasis system and to improve the results of complex treatment in patients with SARS-CoV-2 in the COVID hospital.

Material and methods. From April 2020 to December 2020, 245 patients between the ages of 27 and 89 with SARS-CoV-2 associated pneumonia were treated on the basis of the University Clinical Hospital No. 4 of the First Sechenov Moscow State Medical University (Sechenov University) of the Ministry of Health of the Russian Federation. The average age of the patients was 56.7±4.2 years. The gender distribution was as follows: 132 (53.9%) male patients, 113 (46.1%) female patients. The vast majority of patients (167 - 68.2%) at the time of admission had one or more comorbidities that worsen the course of COVID-19 associated pneumonia.

According to Table 1, the most common comorbidities were: cardiac diseases, obesity and diabetes mellitus. The majority of patients have two or more comorbidities.

All patients were examined clinically, instrumentally and using laboratory tests. The severity of fever (an increase in body temperature above 37.5 C) was assessed at admission and during treatment, and the level of respiratory failure was determined using a pulse oximeter (SpO_2).

Upon admission all patients underwent a PCR test. The volume and nature of changes in the pulmonary parenchyma against the background of viral pneumonia were evaluated according to results of computed tomography, which was performed at admission, repeated every 7 days, as well as with the deterioration of the patients' condition (increased respiratory failure, decreased saturation level). In accordance with the Order of the Ministry of Health of the Russian Federation, the severity of viral pneumonia was assessed as CT-2 (more than 3 foci or areas of induration by the type of frosted glass ≤ 5 cm in maximum diameter, involvement of the lung parenchyma 25-50%); CT-3 (induration of the lung tissue by

the type of frosted glass in combination with foci of consolidation, involvement of the lung parenchyma 50-75%); CT-4 (diffuse induration of the lung tissue by the type of "frosted glass" and consolidation in combination with reticular changes, involvement of the lung parenchyma ≥ 75%).

Among the laboratory parameters, lactate dehydrogenase (LDH) was particularly distinguished as a sign of lung tissue destruction, C-reactive protein (CRP), interleukin-6 (IL-6) levels, and the severity of leukopenia and lymphopenia as factors of unfavorable prognosis. Assessment of the hemostatic system in hospitalized patients was performed daily using local coagulation tests (LCT), including APTT, PT, TT, PTI, INR, Fibrinogen, and D-dimer. From the global coagulation tests, an integral coagulation thrombodynamics test was used, which was performed on the 1st, 7th and 14th days 2-3 hours before the next injection of heparin. The main indicators of the thrombodynamics test were: Tlag (lag time, delay time of the beginning of the formation of a fibrin clot), V (clot growth rate), Tsp (time of the emergence of spontaneous clots), D (density of the fibrin clot).

All participating in the study patients were divided by simple randomization into 2 groups that were comparable in terms of gender, age, comorbidities, severity of viral pneumonia, and general condition. The first group included 117 (47.7%) patients, their state of the hemostatic system was assessed and its disorders were corrected using local coagulation tests. The second group included 128 (52.3%) patients, for them, in addition to local coagulation tests, an integral coagulation test was used - the thrombodynamics test- to assess and correct the state of the hemostatic system. Assessment and correction of hemostasis were performed at the control points (1st, 7th, 14th day) of the study, and more often if necessary.

Treatment of all patients with coronavirus infection was carried out comprehensively in accordance with the temporary methodological recommendations of the Ministry of Health of the Russian Federation [2]. Drug therapy included Hydroxychloroquine+azithromycin or mefloquine+azithromycin or Lopinavir/ritonavir+recombinant interferon beta-1b. According to vital indications, due to an uncontrolled immune response, 58 (23.7%) patients of both groups were injected drugs based on monoclonal antibodies that inhibit interleukin-6 (IL-6) receptors once. In parallel, all patients with comorbid pathology received appropriate treatment.

Taking into account the use of hydroxychloroquine, which has cardiotoxicity, all patients were monitored daily by ECG to exclude the development of disorders of the cardiovascular system. Laboratory monitoring of the main blood parameters in all patients was carried out at the time of their admission to the hospital and in the future, as necessary, in the course of treatment.

According to the temporary guidelines of the Ministry of Health of the Russian Federation [2], all patients were prescribed anticoagulant therapy with low-molecular-weight heparins (enoxaparin sodium) in preventive doses - 40 mg/day subcutaneously in the anterior abdominal wall, and taking into account the data of the thrombodynamics test, the dose of anticoagulants was increased to 80-160 mg/day (40 mg or 80 mg 2 times a day). The daily dose of LMWH was adjusted according to the patient's weight, laboratory data, and the presence of comorbidities.

The main points of the study were the time of admission of the patient to the hospital (1 point), the 7th day of treatment (2 point) and the 14th day – (3 point). The thrombodynamics test was performed in group 2 patients at point 1 before the first injection of LMWH, then at points 2 and 3. In the first group, the thrombodynamics test was performed only at point 3.

Statistical data processing was performed using the SPSS program for Windows, version 17. The results are presented as an average±standard deviation. The differences between the groups were analyzed using a bilateral Student test for normally distributed data. The statistically significant value was assumed to be $p<0.05$.

Results and discussion. At the time of admission to the clinic, the general condition was stated as severe in 212 (86.9%) patients, the condition of moderate severity - in 33 (13.1%) patients. No patients needed artificial lung ventilation (ALV). Standard O_2 therapy was prescribed to 215 patients, noninvasive ventilation of lungs (NIVL) - to 30 patients.

A positive result of treatment was established with a positive dynamics of the patient's condition, a decrease in the area of lung tissue damage, normalization of laboratory parameters, including a decrease in the level of D-dimer when he was discharged from the hospital. A negative result of treatment was determined when the patient's condition worsened, viral pneumonia progressed according to CT data, respiratory failure increased (SpO_2 level decreased), the patient was transferred to ALV, and in the case of a fatal outcome of the disease.

The results of patients' treatment in the first and second groups were different. The dynamics of the main clinical indicators against the background of treatment in patients of both groups is presented in Table 2.

Table 2 data shows that both groups were comparable in clinical symptoms and severity of the disease at the time of treatment initiation.

The dynamics of the CT data of lungs and of the severity of the patient's conditions in both groups during observation are presented in Figures 1 and 2.

Table 1. Comorbidities in patients with SARS-CoV-2 (n=245)

Comorbidities	Number of patients	
	Abs.	%
Cardiac pathology	121	49.5
Oncological diseases	36	14.6
Type 2 diabetes mellitus	96	39.2
Obesity	102	41.7
Pulmonary diseases	40	16.2
Atherosclerosis	34	13.9

Table 2. Dynamics of clinical indicators in patients of both groups

Clinical aspects / Amount		At the time of admission		The 7th day of inpatient treatment		The 14th day of inpatient treatment	
		Group 1 (n=117)	Group 2 (n=128)	Group 1 (n=109)	Group 2 (n=123)	Group 1 (n=102)	Group 2 (n=123)
Fever, °C		117 (100)	128 (100)	76 (69.7)	18 (14.6)	-	-
Dyspnea		102 (87.2)	109 (85.2)	98 (89.9)	54 (43.9)	34 (33.3)	13 (10.5)
SpO2, %	≤90	24 (20.5)	22 (17.2)	49 (44.9)	18 (14.6)	17 (16.7)	-
	≤95	83 (71)	89 (69.5)	42 (38.5)	66 (53.7)	34 (33.3)	10 (8.2)
	More than 95	10 (8.5)	17 (13.3)	18 (16.6)	39 (31.7)	51 (50.0)	113 (91.8)
CT 1		-	-	7 (6.4)	24 (19.5)	38 (37.2)	68 (55.3)
CT 2		85 (72.6)	90 (70.3)	64 (58.7)	61 (49.6)	35 (34.4)	44 (35.8)
CT 3		32 (27.4)	38 (29.7)	28 (25.7)	30 (24.4)	22 (21.6)	11 (8.9)
CT 4		-	-	10 (9.2)	8 (6.5)	7 (6.8)	-
Severity of patient's condition	Mild degree			6 (5.5)	14 (11.4)	71 (69.6)	102 (82.9)
	Moderate degree	13 (11.2)	20 (15.6)	31 (28.4)	56 (45.5)	17 (16.7)	16 (13.0)
	Severe degree	104 (88.8)	108 (84.4)	72 (66.1)	53 (43.1)	14 (13.7)	5 (4.1)
Fatal outcome		-	-	8 (6.8)	5 (3.9)	7 (6.4)	-

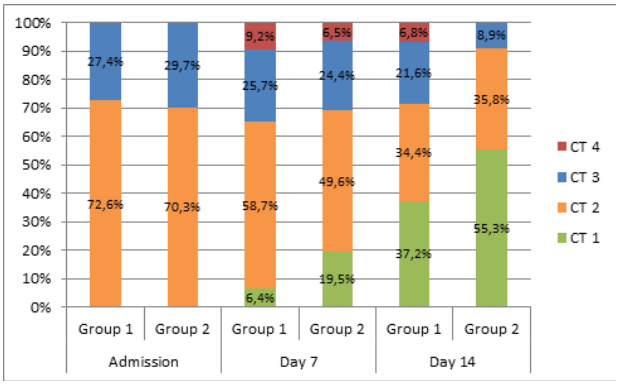

Fig. 1. Dynamics of lung injury area based on CT scans

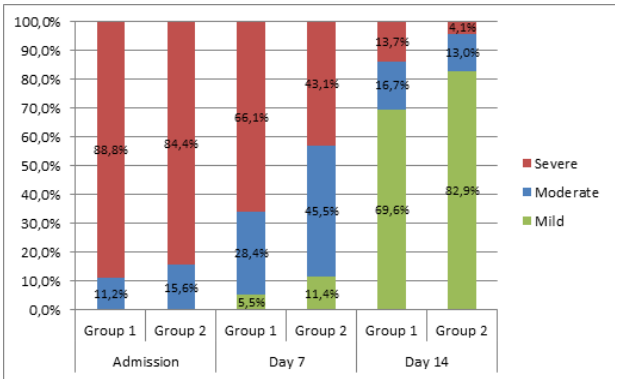

Fig. 2. Dynamics of severity of patient's condition

Positive dynamics of clinical symptoms was detected 1.8 times more often in patients of the 2-nd group than in the 1-st group ($p<0.05$). Fever and shortness of breath in the 2-nd group decreased faster, the SpO_2 index recovered more rapidly, especially in patients with severe hypoxia (with $SpO_2<90$), the number of patients with moderate and severe severity to the third point of the study in the 2-nd group was 1.8 times less than in the 1-st group ($p<0.05$). The number of patients with severe lung lesions (CT-3 and CT-4) by the third point of the study was detected in the 2-nd group 3.2 times less often ($p<0.01$) compared to the 1-st group.

The number of deaths by the end of the study in the 1-st group exceeded the indicators in the 2-nd group by 3.3 times ($p<0.01$), and all these patients have the lung lesion area corresponded to CT-4 stage.

Most of the patients (183 patients) were discharged on the 14th-15th day for outpatient follow-up treatment with recommendations, so the study was completed at the 3rd point. The remaining patients continued inpatient treatment and were discharged at a later date. Average bed-day in the 2-nd group (15±1.6 days) was by 1.6 times shorter than in the 1-st group (24±7.2 days). Hemorrhagic complications were not registered, despite the therapeutic doses of LMWH in patients of 2-nd group.

The results of the hemostasis state of patients of both groups against the background of the treatment are presented in Table 3.

According to Table 3, all 245 patients at admission (1 point) had a high level of D-dimer, that was regarded as a state of hypercoagulation and was required the appointment of anticoagulants. At the same time, the dependence of D-dimer level on the area of lung damage was revealed. The level of D-dimer was higher in patients with a large percentage of lung tissue damage.

In 98 (83.8%) patients of the 1-st group at admission (1 point), moderate hypercoagulation was indicated by a number of LCT data, in particular, a decrease in PT, an increase in PTI and fibrinogen. In group 2, the thrombodynamics test confirmed the state of hypercoagulation at the time of admission in all 128 (100%) patients. At the same time, 50 of them (39%) showed expressed hypercoagulation with the formation of spontaneous clots. Taking into account the data obtained during the thrombodynamics test, all patients in this group were prescribed therapeutic doses of LMWH (78 patients - 80 mg/day (40 mg 2 times a day), and 50 patients - 160 mg/day (80 mg 2 times a day).

Table 3. Results of the state of hemostasis in both groups of patients

Indicator		Reference values	At the time of admission		The 7th day of inpatient treatment		The 14th day of inpatient treatment	
			Group 1 (n=117)	Group 2 (n=128)	Group 1 (n=109)	Group 2 (n=123)	Group 1 (n=102)	Group 2 (n=123)
INR		0.8-1.3	1.0±0.5	0.9±0.57	1.1±0.2	1.25±0.3	0.8±0.1	0.9±0.5
PT		11-16 sec	6±2.4	9±2.7	10±1.1	12±1.17	14±2.6	17±0.5
PTI		80-120%	120±5.8	121±5.7	101±2.8	82±2.7	83±1.2	65±1.2
TT		14-21 sec	14±0.9	13±0.8	17±1.4	20±1.4	21±0.7	22±0.9
APTT		25-39 sec	23±0.3	22±0.45	37±1.7	37±2.8	40±0.3	43±0.5
Fibrinogen		1.8-3.5 g/l	4.6±0.7	4.3±0.9	3.7±0.5	3.3±1.3	3.5±0.3	3.1±0.2
D-dimer		up to 250 ng/ml	2377± 979.385	2671± 1030.125	1714± 573.779	1672± 628.757	1043± 415.287	983± 292.975
Thrombo-dynamics test	Tlag	0.6-1.5 min		0.68±0.26		0.9±0.24	0.94±0.31	1.16±0.23
	V	20-29 mkm/ min		31.85±2.54		18.08±3.12	32±3.8	16.84±2.43
	Tsp	>30 min		22.57±3.26		≥30	29,22±3,5	no
	D	15000-32000 c.u.		34585± 3229.25		27769± 3925.36	33164± 3641.52	-

On the 7th day of complex therapy (point 2) according to the D-dimer level, all patients of both groups remained in a state of hypercoagulation. While other LCT in the 1-nd group patients determinated moderate hypo - or normal coagulation in all cases but in despite of treatment 10 patients noted a deterioration in their condition (increased of dyspnea, decreased oxygen saturation, etc.). In 8 (6.8%) patients to the 2nd control point, against the background of negative dynamics of the condition, fatal outcomes were noted.

At the same point, all 123 patients in the 2nd group were in a state of normal and hypocoagulation, according to LCT data. At the same time, despite the positive dynamics of the D-dimer level, it remained increased in all patients. The integral thrombodynamics test showed that the majority of patients (93-75.6%) were in a state of moderate hypo - and normal coagulation. In 25 (20.5%) patients, a state of moderate hypercoagulation (expressed in excess of the V index to 32-33 microns/min) was detected, and in 5 (3.9%) patients - expressed hypercoagulation with the formation of spontaneous clots. They showed negative dynamics of treatment (progression of respiratory failure, decreased oxygen saturation, transfer to artifical lung ventilation), which could be associated with the progression of viral pneumonia. They adjusted the therapeutic dose of LMWH. By the 2nd point of the study, 5 deaths were noted in group 2 (3.9%).

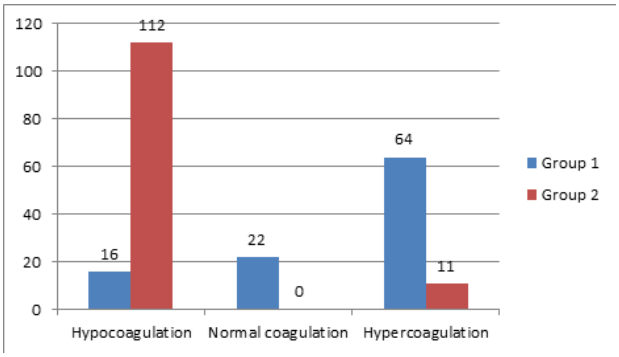

Fig. 3. Coagulation state of patients according to Thrombodynamics test on 14th day of treatment

By the 14th day of inpatient treatment (point 3), all 102 patients of group 1 were found to have hypo-and normal coagulation, while the increased D-dimer level remained in all patients. However, the use of the integral global thrombodynamics test revealed a state of hypercoagulation in 64 patients of this group (including 26 patients preparing for discharge from the hospital); with the emergence of spontaneous fibrin clots in 11 patients, a state of normal coagulation was detected in 22 patients, and only 16 patients were in a state of moderate hypocoagulation (Fig. 3).

The majority of patients in the 1st group (71 patients – 60.7%) with positive treatment dynamics were discharged for outpatient follow-up treatment on the 14th -15th day. Everyone was recommended to take preventive doses of oral anticoagulants (OACs) for up to a month. The data obtained by the thrombodynamics test allowed recommending prolonged use of anticoagulants to 26 patients. Negative dynamics of treatment by the 14th day was found in 38 patients of this group. They continued to be treated in a hospital. In 31 patients, the dose of LMWH was adjusted taking into account the data of the thrombodynamics test, which helped to improve their condition and further discharge for outpatient follow-up treatment. By the 3rd point of the study, 7 patients of the 1-st group had a fatal outcome. The overall mortality rate in the first group of patients was 15 (12.8%) cases.

On the 14th day of inpatient treatment in 112 patients of the 2-nd group, according to the thrombodynamics test, a state of hypocoagulation (V<20 microns/min) was detected, and according to LCT - in all patients, however, the level of D-dimer again remained increased in all patients. All 112 patients had the positive results of treatment, and they were discharged for outpatient follow-up treatment with recommendations for taking oral anticoagulants (OACs) in the recommended therapeutic doses for three months. Other 11 patients with status of moderate hypercoagulation (V>30 microns/min) according to the thrombodynamics test, were continued treatment in the hospital due to the severity of the disease. Later, all of them were discharged for outpatient follow-up treatment with recommendations for prolonged (up to 3-6 months) taking of OACs. The mortal cases during last period in this group were not registrated.

Thus, the results of treatment of patients in the group with hemostasis control using the global coagulation thrombody-

namics test were statistically significantly better. The number of patients who passed during treatment to a more severe stage of the disease in the 2-nd group was by 1.8 times less than in the 1-st group ($p<0.05$), the number of deaths was by 3.3 times less ($p<0.01$), the number of patients with severe lung lesions (CT-3 and CT-4) by the third point of the study was detected in the 2-nd group by 3.2 times less often ($p<0.01$) compared to the 1-st group. Average bed-day in the 2-nd group patients (15±1.6 days) was by 1.6 times shorter ($p<0.05$) than in the 1-st group (24±7.2 days). The dynamics of regression of the D-dimer level was much more noticeable. At the same time, the dependence of the negative dynamics of treatment of patients with COVID infection, including fatal outcomes, on the detected hypercoagulation, determined by the integral coagulation thrombodynamics test, was established.

Despite the use of the developed treatment regimens for patients with coronavirus, the results of therapy are far from ideal. The significant amount of severe forms of the disease and a high mortality rate are actual . The study showed the need for a comprehensive approach to the treatment of each patient, taking into account their individual characteristics, the state of hemostasis and comorbidities.

Hospitalized patients with confirmed coronavirus had different comorbid status. The presence of diabetes mellitus, cardiovascular pathology, metabolic syndrome, etc. initially worsened the prognosis of treatment, both for the pathology they had and for the COVID infection that had joined. These patients reacted worse to treatment, showed negative dynamics of the course of the disease, more often moved to a more severe form of the disease, more often needed non-invasive ventilation of lungs (NIVL) and ended up on a ALV, and as a result, more patients were added to the numbers of fatal outcomes of treatment.

The so-called "cytokine storm" that develops in the patient's body is a consequence of the simultaneous avalanche-like activation of multidirectional proteases, the kinin-kallikrein system, as well as pro- and anti-inflammatory cytokines, primarily the pro-inflammatory cytokines interleukin-1 and interleukin-6 in the blood of patients with COVID-19. To suppress the "cytokine storm", monoclonal inhibitors of interleukin-1 and interleukin-6 are used, steroid hormones are used as immunosuppressive agents, but all of them have a narrow range of clinical applications and it is more justified at the beginning of the development of the "cytokine storm".

It is not unreasonable to assume that the deterioration of the patients' condition is a direct consequence of microcirculation disorders both in the lung tissue and in the periphery, which are prolonged by hypercoagulative syndrome and microthrombosis of arterioles and venules. In turn, hypercoagulative syndrome is directly associated with the development of a "cytokine storm", with the effect of the virus on the vascular endothelium, causing their thrombosis – thrombosis of small lung vessels is confirmed by autopsy data [18]. Autoimmune inflammation of the vascular endothelium with typical microthrombosis in the kidneys, intestines, heart, etc. was proven. It is the development of coagulopathies already in the early stages of COVID-19 that allows attributing this disease to prothrombotic conditions that require active anticoagulant therapy.

The concentration of D-dimer in the blood is the second important biomarker of great importance in the case of suspected venous thromboembolism (VTE). Some recent studies show that if a patient with COVID-19 has a high level of D-dimer when admitted to the hospital, then the risk of death increases [19]. An increased concentration of fibrinogen and D-dimer in the blood of patients activates hypercoagulation. It is these indicators that are useful in assessing the severity of a patient with SARS-CoV-2 and are usually used to diagnose or exclude thrombotic processes, such as deep vein thrombosis or pulmonary embolism (PE).

In almost all patients admitted to the clinic with confirmed SARS-CoV-2, standard laboratory parameters reflecting the state of the hemostatic system were within the reference values, while increased, sometimes to high numbers, D-dimer values were detected. Based on the increase in this indicator, all patients were diagnosed with hypercoagulation and were prescribed anticoagulants. This is practically justified and appropriate, taking into account the peculiarities of the pathogenesis of COVID infection. However, it is necessary to take into account the fact that the D-dimer level indicator is highly sensitive to any inflammatory process in the body, with very low specificity. In each patient with COVID-pneumonia, in response to the developing massive inflammation in the lung tissue, the level of D-dimer sharply increases, and its values depend on the area of lung damage and the severity of the patient's condition. In these circumstances, there is no complete confidence in the quality of the definition of hypercoagulative syndrome based on the data of the D-dimer level alone. This is confirmed by the dynamics of the D-dimer level against the background of anticoagulant therapy in patients with COVID-pneumonia. A gradual decrease in the values of the D-dimer, while maintaining a sufficiently high reading, even in the presence of normal coagulation detected by the global thrombodynamics test, may indicate that this indicator is maintained by the inflammatory process in the lungs.

It should be understood that the D-dimer is not a harbinger, but an indicator of a thrombotic event that has already occurred in the body. In our study, these are multiple microthrombosis at the level of microcirculation both in the lung tissue and on the periphery. An increased D-dimer is an increase in the level of fibrin degradation products during the lysis of an already formed fibrin clot, therefore, this analysis is not sufficient to prevent a thrombotic event. The prognosis requires the results of global coagulation tests, which make it possible to assess the hemostatic system as a whole at a specific time. Thus, the integral coagulation thrombodynamics test allows assessing the state of the patient's plasma hemostasis at the time of the test and to monitor the growth of a fibrin clot in real time, which reflects the holistic picture of its coagulation system and to adjust the dosage of anticoagulants for the successful prevention of a thrombotic event.

The study showed that in the group of patients in which anticoagulant therapy was adjusted based on the data of the thrombodynamics test, they received more positive treatment results, and in a larger number of patients they managed to achieve a state of normal and hypocoagulation. Patients were statistically significantly less likely to develop more severe forms of the disease, were less likely to be on ALV, and fewer deaths were reported. Naturally, by the time of discharge from the hospital, the majority of patients in both groups retained elevated levels of D-dimer, and hypercoagulation detected in a number of patients by the global thrombodynamics test required prolongation of anticoagulant therapy at the outpatient stage of treatment.

Thus, the results of the study showed the need for an individual approach when choosing a comprehensive treatment regimen in all patients, especially in those with a burdened comorbid background. The severity of the patients' condition and the dynamics of their symptoms during treatment depend on the state of microcirculation in the lungs and on the periphery and the volume of their thrombotic lesion. Anticoagulant therapy

prescribed as early as possible in adequate therapeutic doses (UFH, LMWH) in all patients with a confirmed diagnosis of SARS-CoV-2 with associated viral pneumonia allowed achieving generally positive treatment results. It should be noted that the global coagulation thrombodynamics test is highly effective for timely assessment and correction of the state of the hemostatic system (hypercoagulation syndrome, state of thrombotic readiness and prevention of PE) in the course of treatment in this group of patients.

Conclusions. The state of microcirculation in the lungs and on the periphery and the degree of its thrombotic damage determine the severity of the condition of patients with SARS-CoV-2 and affect the prospects for their treatment.

Local coagulation tests (LCT) and the level of D-dimer do not always reflect the state of hypercoagulation in patients with SARS-CoV-2 adequately and are dependent on the degree of lung damage, which may affect the tactics and results of treatment.

The integral coagulation thrombodynamics test showed high informativity for the prevention of VTE and for the correction of hemostasis in patients with SARS-CoV-2.

Timely correction of anticoagulant therapy based on the data of the global coagulation thrombodynamics test allowed improving the results of complex treatment in almost one fifth of patients with SARS-CoV-2 infection.

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SUMMARY

ROLE OF THROMBODYNAMICS GLOBAL COAGULATION TEST IN IMPROVING TREATMENT RESULTS IN PATIENTS WITH CORONAVIRUS INFECTION AT A COVID-19 HOSPITAL

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The aim of the study was to evaluate the effectiveness of the global coagulation test of thrombodynamics for monitoring and correcting the hemostatic system and improving the results of complex treatment in patients with SARS-CoV-2 in the COVID hospital.

From April 2020 to December 2020 on the basis of the University Clinical Hospital No. 4 of the First Moscow State Medical University named I.M. Sechenov (Sechenov University) of the Ministry of Health of the Russian Federation 245 patients between the ages of 27 and 89 with SARS-CoV-2 associated pneumonia were treated. The mean age of the patients was 56.7 ± 4.2 years. All patients participating in the study were divided by simple randomization into two groups. The volume of lesion of the lung parenchyma was assessed according to the data of com-

puted tomography. All patients were treated for SARS-CoV-2 in a comprehensive manner in accordance with the temporary guidelines of the Ministry of Health of the Russian Federation with the mandatory prescription of low molecular weight heparins (LMWH). Assessment and correction of the hemostasis system in 177 patients (47.7%) of group 1 was carried out daily using local coagulation tests (LCT), including APTT, PT, TT, PTI, INR, Fibrinogen and D-dimer level. The second group included 128 patients (52.3%), who, in addition to local coagulation tests, used the integral coagulation test - the thrombodynamics test- to assess and correct the state of the hemostatic system. Assessment and correction of hemostasis were performed at the control points (1, 7, 14 days) of the study.

Compared to LCT, the thrombodynamics test reliably more often revealed the state of hypercoagulability, which was promptly corrected by increased doses of LMWH in group 2. Positive dynamics of clinical symptoms were detected in patients of group 2 1.8 times more often than in group 1 ($p<0.05$): fever and shortness of breath in group 2 decreased faster, the SpO_2 index recovered more rapidly, especially in patients with severe hypoxia (with $SpO_2<90$), the number of patients with moderate and severe severity by the third point of the study in group 2 was 1.8 times less than in group 1 ($p<0.05$). Severe forms of lung damage (CT-3 and CT-4) were detected in group 2 3.2 times less frequently ($p <0.01$) compared with group 1, and the number of deaths was 3.3 times less frequent ($p<0.01$) by the end of the study. The average bed-day in group 2 of patients (15±1.6 days) was 1.6 times shorter than in group 1 (24±7.2 days). Hemorrhagic complications were not recorded, despite the therapeutic doses of LMWH in patients of group 2.

The severity of the condition of patients with SARS-CoV-2 and the dynamics of their symptoms depend on the state of microcirculation in the lungs and in the periphery and on the volume of thrombotic lesions. Anticoagulant therapy prescribed as early as possible in adequate therapeutic doses in patients with SARS-CoV-2 associated viral pneumonia made it possible to achieve positive treatment results. The use of the global coagulation thrombodynamics test has shown high efficiency for the timely assessment and correction of the state of the hemostasis system.

Keywords: coronavirus infection, hypercoagulable syndrome, anticoagulant therapy, thrombodynamics test.

РЕЗЮМЕ

ВОЗМОЖНОСТИ ГЛОБАЛЬНОГО ТЕСТА ТРОМБОДИНАМИКИ ДЛЯ УЛУЧШЕНИЯ РЕЗУЛЬТАТОВ ЛЕЧЕНИЯ БОЛЬНЫХ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ В УСЛОВИЯХ COVID-СТАЦИОНАРА

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ФГАУ ВО Первый МГМУ им. И.М. Сеченова (Сеченовский Университет), Россия

Цель исследования – оценить эффективность использования глобального коагуляционного теста тромбодинамики для контроля и коррекции системы гемостаза и улучшения результатов комплексного лечения у пациентов с SARS-CoV-2 в COVID-стационаре.

С апреля по декабрь 2020 года на базе Университетской клинической больницы №4 Первого МГМУ им. И.М. Сеченова (Сеченовский Университет) МЗ РФ пролечено 245 пациентов с SARS-CoV-2 ассоциированной пневмонией в возрасте от 27 до 89 лет. Средний возраст – 56,7±4,2 г. Всех больных методом простой рандомизации разделили на две группы. Объем поражения паренхимы легких оценивали по данным компьютерной томографии. Лечение всех больных по поводу SARS-CoV-2 проводили комплексно в соответствии с временными методическими рекомендациями МЗ РФ с обязательным назначением низкомолекулярных гепаринов (НМГ). Оценку и корректировку системы гемостаза у 177 (47,7%) больных I группы проводили ежедневно при помощи локальных коагуляционных тестов (ЛКТ), включавших АЧТВ, ПВ, ТВ, ПТИ, МНО, фибриноген и уровень Д-димера. Во II группу включено 128 (52,3%) пациентов, которым, помимо ЛКТ, применяли интегральный коагуляционный тест - тест тромбодинамики, на основании данных которого корректировали дозу НМГ. Оценку и корректировку гемостаза проводили в контрольных точках исследования на 1, 7, 14 сутки.

В сравнении с ЛКТ, тест тромбодинамики достоверно чаще выявлял состояние гиперкоагуляции, которое своевременно скорректировано повышенными дозами НМГ во II группе. Положительная динамика клинических симптомов выявлена у них в 1,8 раза чаще, чем в I группе ($p<0,05$): лихорадка и одышка уменьшались быстрее, SpO_2 восстанавливался более быстрыми темпами, особенно при $SpO_2<90$, на 14 сутки количество больных средней и тяжелой степени тяжести во II группе было в 1,8 раза меньше, чем в I группе ($p<0,05$). Тяжелые формы поражения легких (КТ-3 и КТ-4) выявлены во II группе в 3,2 раза реже ($p<0,01$) в сравнении с I группой, а количество летальных исходов - в 3,3 раза реже ($p<0,01$) к концу исследования. Средний койко-день во II группе больных (15±1,6 дней) был в 1,6 раза меньше, чем в I группе (24±7.2 дня). Несмотря на лечебные дозы НМГ у пациентов II группы геморрагических осложнений не зарегистрировано.

Тяжесть состояния больных SARS-CoV-2 и динамика их симптомов зависят от состояния микроциркуляции в легких и на периферии и от объема тромботического поражения. Максимально рано назначенная в адекватных лечебных дозах антикоагулянтная терапия у пациентов с SARS-CoV-2 ассоциированной вирусной пневмонией позволила добиться положительных результатов лечения. Применение глобального коагуляционного теста тромбодинамики позволило своевременно оценить и эффективно скорректировать состояние системы гемостаза.

რეზიუმე

გლობალური თრომბოდინამიკის ტესტის შესაძლებლობები კორონავირუსული ინფექციით დაავადებულ პაციენტთა მკურნალობის შედეგების გასაუმჯობესებლად COVID-სტაციონარის პირობებში

ა.კრილოვი, ტ.ხორობრიხი, ა.პეტროვსკაია, ს.ხმიროვა, ვ.აგაჯანოვი, ნ.ხუსაინოვა

უმაღლესი განათლების ფედერალური სახელმწიფო ავტონომიური საგანმანათლებლო დაწესებულება ი. სეჩენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი),რუსეთი

კვლევის მიზანს წარმოადგენდა თრომბოდინამიკის გლობალური კოაგულაციური ტესტის გამოყენების ეფექტურობის შეფასება ჰემოსტაზის სისტე-

მის კონტროლისა და კორექციისთვის, კომპლექსური მკურნალობის შედეგების გასაუმჯობესებლად SARS-CoV-2 პაციენტებში COVID-სტაციონარში.

2020 წლის აპრილიდან დეკემბრამდე რფ ჯანდაცვის სამინისტროს ი. სეჩენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტის (სეჩენოვის უნივერსიტეტი) №4 საუნივერსიტეტო კლინიკურ საავადმყოფოს ბაზაზე მკურნალობა ჩაუტარდა 27-დან 89 წლამდე ასაკის 245 პაციენტს SARS-CoV-2 ასოცირებული პნევმონიით. საშუალო ასაკი - 56,7±4,2 წ. ავადმყოფები დაიყო ორ ჯგუფად მარტივი რანდომიზაციის მეთოდით. ფილტვების პარენქიმის დაზიანების მოცულობა შეფასდა კომპიუტერული ტომოგრაფიის მონაცემებით. ყველა პაციენტს SARS-CoV-2-ის მკურნალობა ჩაუტარდა კომპლექსურად, რფ ჯანდაცვის სამინისტროს დროებითი სახელმძღვანელო რეკომენდაციების შესაბამისად დაბალი მოლეკულური წონის ჰეპარინების (დმწჰ) სავალდებულო დანიშვნით. ჰემოსტაზის სისტემის შეფასება და კორექცია I ჯგუფის 177 (47.7%) პაციენტში ხდებოდა ყოველდღიურად ლოკალური კოაგულაციური ტესტების გამოყენებით, მათ შორის: აქტივირებული ნაწილობრივი თრომბოპლასტინის დრო, თრომბინის დრო, პროთრომბინის ინდექსი, საერთაშორისო ნორმალიზებული თანაფარდობა, ფიბროგენი და დ-დიმერის დონე. II ჯგუფი შეადგინა 128 (52,3%) პაციენტმა, რომელთათვის, ლოკალური კოაგულაციური ტესტების გარდა, გამოყენებული იყო ინტეგრალური კოაგულაციური ტესტი - თრომბოდინამიკის ტესტი, რომლის საფუძველზეც ხდებოდა დაბალი მოლეკულური ჰეპარინების დოზის კორექტირება. ჰემოსტაზის კვლევის შეფასება და კორექტირება ჩატარდა კვლევის საკონტროლო პუნქტებში პირველ, მეშვიდე, მეთოთხმეტე დღეს.

ლოკალური კოაგულაციური ტესტების შედარებით, თრომბოდინამიკის ტესტი საიმედოდ უფრო ხშირად ავლენდა ჰიპერკოაგულაციის მდგომარეობას, რომელიც იყო დაუყოვნებლივ კორექტირებული დაბალი მოლეკულური ჰეპარინების გაზრდილი დოზებით II ჯგუფში. კლინიკური სიმპტომების დადებითი დინამიკა მათში 1,8-ჯერ უფრო ხშირად გამოვლინდა, ვიდრე I ჯგუფში ($p<0,05$): ციება და ქოშინი უფრო სწრაფად შემცირდა, SpO_2 უფრო სწრაფად აღდგა, განსაკუთრებით, როდესაც $SpO_2<90$, საშუალო და მძიმე სიმძიმის მქონე პაციენტების რაოდენობა II ჯგუფში 1,8-ჯერ ნაკლები იყო, ვიდრე I ჯგუფში ($p<0,05$) მეთოთხმეტე დღეს. ფილტვების დაზიანების მძიმე ფორმები (კტ-3 და კტ-4) II ჯგუფში გამოვლინდა 3,2-ჯერ უფრო იშვიათად ($p<0,01$) I ჯგუფთან შედარებით, ხოლო ლეტალური დასასრულის რაოდენობა - 3,3-ჯერ იშვიათად ($p<0,01$) კვლევის ბოლოს. პაციენტების II ჯგუფში საშუალო საწოლის დღე (15±1,6 დღე) 1,6-ჯერ ნაკლები იყო, ვიდრე I ჯგუფში (24±7,2 დღე). დაბალი მოლეკულური წონის ჰეპარინების თერაპიული დოზების მიუხედავად, II ჯგუფის პაციენტებში ჰემორაგიული გართულებები არ დაფიქსირდა.

SARS-CoV-2 დაავადებული პაციენტების მდგომარეობის სიმძიმე და მათი სიმპტომების დინამიკა დამოკიდებულია ფილტვებში და პერიფერიაზე მიკროცირკულაციის მდგომარეობაზე და თრომბოზული დაზიანების მოცულობაზე. მაქსიმალურად ადრე დანიშნული ანტიკოაგულანტული თერაპია ადეკვატურ სამკურნალო დოზებში SARS-CoV-2-თან ასოცირებულ ვირუსულ პნევმონიით დაავადებულ პაციენტებისათვის შესაძლებელს ხდის მკურნალობის დადებით შედეგების მიღწევას. თრომბოდინამიკის გლობალური კოაგულაციური ტესტის გამოყენებამ გამოავლინა მაღალი ეფექტურობა ჰემოსტაზის სისტემის მდგომარეობის დროულ შეფასებასა და კორექციაში.

LASER THERMAL ABLATION OF BENIGN THYROID NODULES AS AN EFFECTIVE, SAFE AND MINIMALLY INVASIVE METHOD FOR TREATING NODULAR GOITER (REVIEW)

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Thyroid nodules (nodules of the thyroid gland — TG) are a fairly common pathology. By the age of 80, about 80% of people have one or more nodules in the TG, but the vast majority of them are benign. Most of the newly discovered nodules are not clinically relevant to the patient, since they are not malignant and do not show any symptoms. The risk of developing carcinoma among all nodules in the TG is 1-10% [22]. Most benign nodules are not fatal to the human body and do not require any special treatment; however, when a compression syndrome or cosmetic defect occurs, treatment is necessary, including surgery [4, 13, 18, 23]. Nevertheless, even if at the time of detection the nodule in the TG does not have a clinically significant effect on the patient's quality of life, there is a possibility that it will appear in the future. Thus, according to the data of Russian and foreign authors, most nodules increase in size [2, 43], which in the future can lead to the formation of compression syndrome. E.K. Alexander showed that an increase in the size of nodules by more than 15% over 5 years occurred in 89% of observations [2]. Approximately 5% of long-term colloidal nodules can lead to the formation of functional autonomy and the development of thyrotoxicosis, effective treatment for which is the removal of hyperfunctioning TG tissue [21].