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CHARACTERISTICS OF THE STUDY GROUP AND DYNAMICS OF PATHOGENETIC MARKERS ON THE BACKGROUND OF DIFFERENT ANTI-COAGULATION MODES

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ABSTRACT

The efficacy of three modes of anticoagulant therapy (direct oral anticoagulant, hepatic heparinized, non-fractionated heparinized) was studied. It was found that with a comparable anti-inflammatory effect of standard therapy with the inclusion of an anticoagulant, low molecular weight heparin significantly more pronouncedly reduces the concentration of the thrombus formation marker D dimer in the peripheral blood; All studied anticoagulation regimens significantly reduce the risk of thrombosis of the PA branches, with a more pronounced effect of low-molecular-weight heparin established; markers of resistance to anticoagulant therapy were found in patients with COVID-19 against the background of type 2 diabetes:

hyperglycemia, greater volume of pulmonary parenchymal lesions, and pancreatic dilatation.

KEYWORDS: *Hyperglycemia, Non-Fractionated, Anticoagulation, Molecular*

INTRODUCTION

The mechanisms involved in the development of immunothrombosis are supported by angiotensin receptor-mediated damage to the alveolar and vascular endothelium. Violation of the structural and functional state of the endothelium is associated with contact damage by neutrophilic extracellular fibers and polyphosphates of microorganisms that activate platelets, plasma cells and factor XII. Other mechanisms involved are systemic activation of complement (both alternative and lectin pathways) and pathogen-associated molecular pattern [7,11]. These changes are accompanied by the hypofibrinolytic status of the alveolar space, which is associated with an increase in the release of the concentration of the plasminogen activator inhibitor by the pulmonary epithelium and endothelial cells. Activation of endothelial cells triggered by the pro-inflammatory cytokines IL-1, IL-6 and hypoxia due to ARDS. Endothelial dysfunction plays an important role in coagulopathy associated with COVID-19, due to an increase in the expression of tissue factor by immune cells and a displacement of the coagulation cascade towards hypercoagulability [1,4]. The cytokine storm induced by SARS-CoV2 infection also stimulates the activation of the coagulation cascade by overexpression of the proinflammatory cytokines IL-1beta and IL-6 [8]. The fibrinolytic system is inhibited by the same immune-mediated mechanisms that activate the coagulation cascade. Platelets are activated by pro-inflammatory cytokines and altered endothelial cells. Endothelial dysfunction associated with inflammation is subsequently exacerbated by activated platelets [6,3].

MATERIALS AND METHODS

During the second phase of the study, 302 patients with moderate, severe and extremely severe forms of COVID-19 with background type 2 diabetes, which have a high risk of thrombosis of the branches of the pulmonary artery, according to the algorithm developed during the first stage of the study. All patients were randomly assigned to 3 groups depending on the anticoagulant therapy regimen.The initial examination, carried out upon admission of patients to the infectious diseases hospital, did not reveal any differences between the groups in terms of the level of glycemia, the concentration of pro-inflammatory markers and a marker of thrombus formation (Table 1). All these parameters significantly exceeded the values typical for healthy individuals ($p < 0.001$ significant difference from CG for all laboratory markers).

RESULTS AND DISCUSSION

All patients as anticoagulant therapy in the treatment regimen included injection low molecular weight heparin (LMWH) in a dose of 0.6 ml once a day, during the first five days of hospitalization. Also, all patients took the antiplatelet agent Dipyridamole 50 mg per day in two doses and the recommended therapy for COVID-19. During the study, the groups were compared in terms of the concentration of markers of systemic inflammation and thrombus formation and the results of echocardiography. During this stage of the study, a risk scale for thrombotic complications of SARS-CoV2 in patients with type 2 diabetes was developed.

TABLE 1 PATIENTS INCLUDED IN THE FIRST STAGE OF THE STUDY

Indicators	Group T + (n = 45)	Group T- (n = 45)	Significant difference between groups
Age, years	55,78±2,85	56,91±2,89	Week
Men (%)	32 (71,11%)	22 (48,89%)	Chi square =4,68*
Volume of lung damage, %	50,48±3,01	50,16±3,01	Week
Disease severity (moderate / severe / extremely severe)	13/20/13	12/21/13	Week
Oxygen saturation of peripheral blood on admission, %	86,12±2,16	88,24±3,12	Week
Duration of type 2 diabetes, years	6,52±0,96	7,01±0,88	Week
Insulin-required state, (%)	18 (40%)	15 (33,33%)	Week
HT, (%)	39 (86,67%)	41 (91,11%)	Week
IHD, (%)	16 (35,56%)	15 (33,33%)	Week
PICS, (%)	8 (17,78%)	10 (22,22%)	Week
Stroke, (%)	3 (6,67%)	2 (4,44%)	Week
CHF III-IV, (%)	12 (26,67%)	11 (24,44%)	Week
CKD C3-4, (%)	7 (15,56%)	5 (11,11%)	Week

TABLE 2 LABORATORY PATHOGENETIC MARKERS IN PATIENTS WITH COVID-19 WITH A HIGH RISK OF THROMBOSIS OF THE BRANCHES OF THE PA ON THE BACKGROUND OF TYPE 2 DIABETES

Indicator	Group R (n=102)	Group H (n=100)	Group LMWH(n=100)	Control group(n=20)
Fibrinogen, g / L	9,03±0,06	8,88±0,07	8,86±0,07	3,11±0,13***
Glucose, mmol / L	10,31±0,30	10,04±0,30	9,81±0,30	5,26±0,14***
MSCT, %	55,82±1,96	53,09±2,00	51,09±1,99	
d dimer, mg / L	4,73±0,21	4,73±0,22	4,70±0,22	0,32±0,03***
Ferritin, ng / ml	1072,44±50,70	1099,11±53,64	1089,44±56,81	73,95±6,15***
IL-6, pg / ml	70,07±3,85	78,90±4,13	81,80±4,14	4,65±0,41***
CRP, mg / L	50,03±1,51	52,07±1,53	52,74±1,49	3,05±0,46***

Note: the reliability of the difference between the groups of patients with COVID-19 + T2DM is unreliable, * - the reliability of the difference between the CG and all patients with COVID-19 + T2DM: three signs - p <0.001.

EchoCG study revealed in patients with COVID-19 with a high risk of thrombosis of the branches of the PA on the background of type 2 diabetes compared with CG, a significant increase in the diameters of the left chambers of the heart: LV (p <0.05) and LA (p <0, 05) with comparable LV systolic function (Table 2). LVMI was significantly increased in the group of

patients compared with CG (p <0.001), confirming its role as a prognostic marker of the risk of thrombosis (described in Chapter 3). and pancreas (p <0.001). The CPR of PA in patients was significantly higher than in the CG (p <0.001), which was accompanied by an increase in the diameter of the pancreas (p <0.001). Echocardiography was comparable in all three groups of patients.

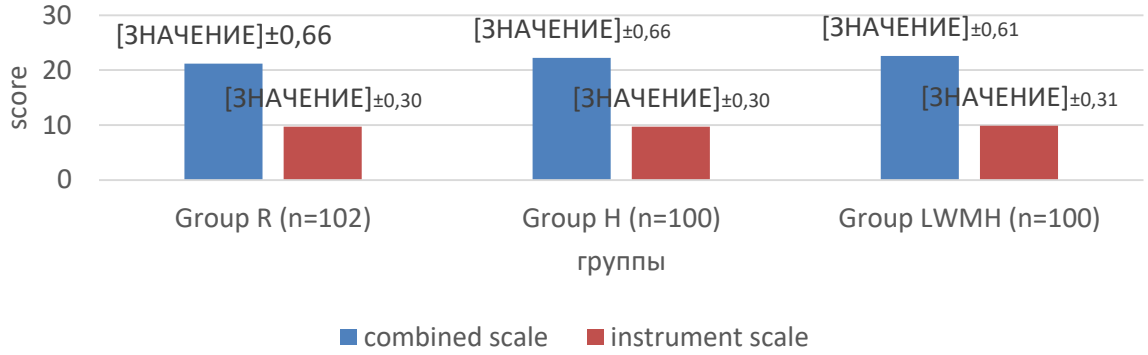
TABLE 3 ECHOCG INDICATORS IN PATIENTS WITH COVID-19 WITH A HIGH RISK OF THROMBOSIS OF THE BRANCHES OF THE PA ON THE BACKGROUND OF TYPE 2 DIABETES

Indicator	Group R (n=102)	Group H (n=100)	Group LMWH (n=100)	Control group(n=20)
LVED, mm	52,87±0,51	51,82±0,53	51,58±0,52	49,15±1,05*
LV mass index, g/m^2	102,90±1,44	103,89±1,53	104,32±1,51	88,15±2,50***
LV EF, %	62,87±0,51	61,82±0,53	61,58±0,52	62,80±1,07
Atrium, mm	37,41±0,42	37,01±0,42	37,03±0,41	34,20±1,05*
Venticle, mm	33,84±0,72	32,40±0,78	31,78±0,77	22,00±0,94***
mPAP, mm Hg	20,05±0,54	19,97±0,55	19,79±0,54	13,35±0,73***
Instrumental scale of risk assessment, score	9,69±0,30	9,72±0,30	9,90±0,31	
Combined risk assessment scale, score	21,19±0,66	22,20±0,66	22,57±0,61	

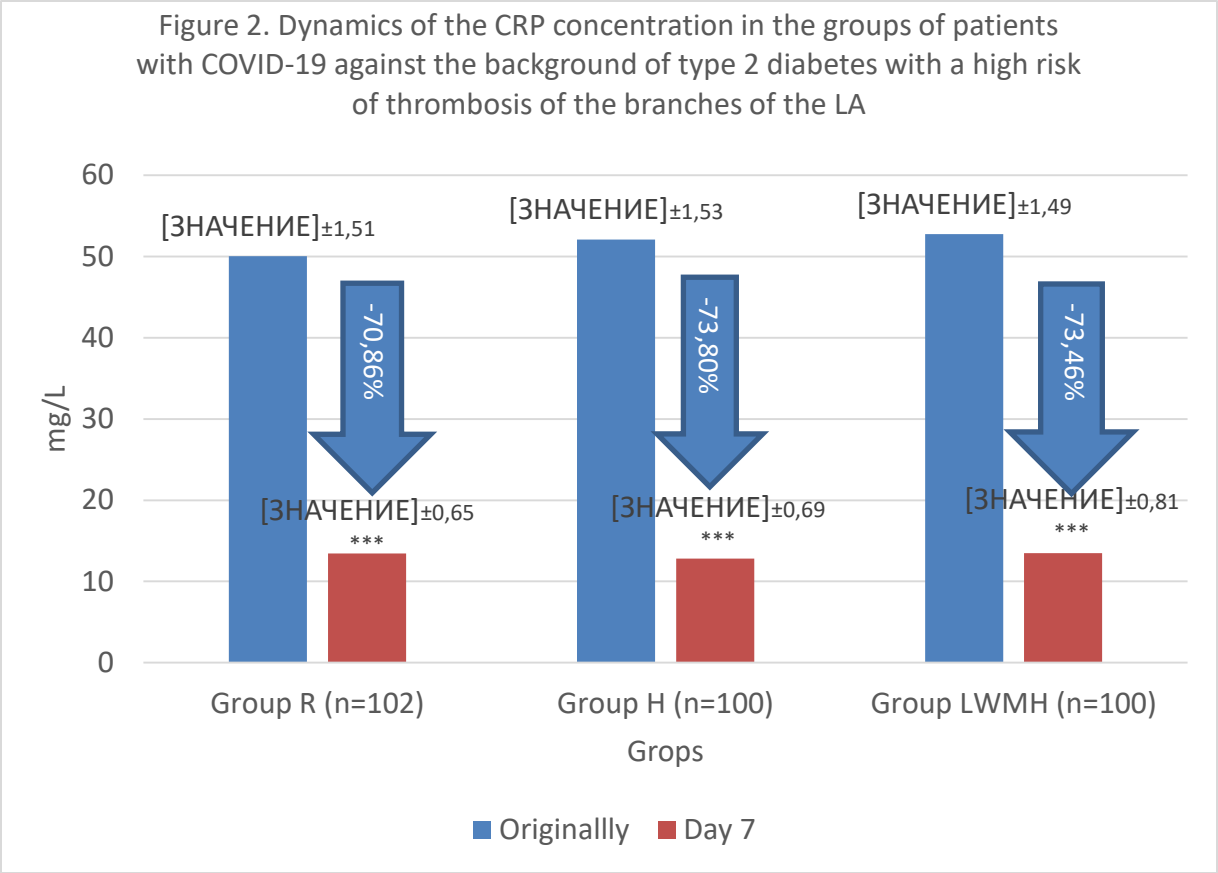
Note: the reliability of the difference between the groups of patients with COVID-19 + T2DM is unreliable, * - the reliability of the difference between the CG and all patients with COVID-19 + T2DM. One sign - p <0.05, three signs - p <0.001.

The score for the risk of thrombosis of the PA branches was also comparable in the comparison groups (Fig. 1) according to the combined and instrumental scales.

Figure 1. Scoring the risk of developing thrombosis of the PA branches in patients with COVID-19 + T2DM with a high risk (intergroup differences are not significant)



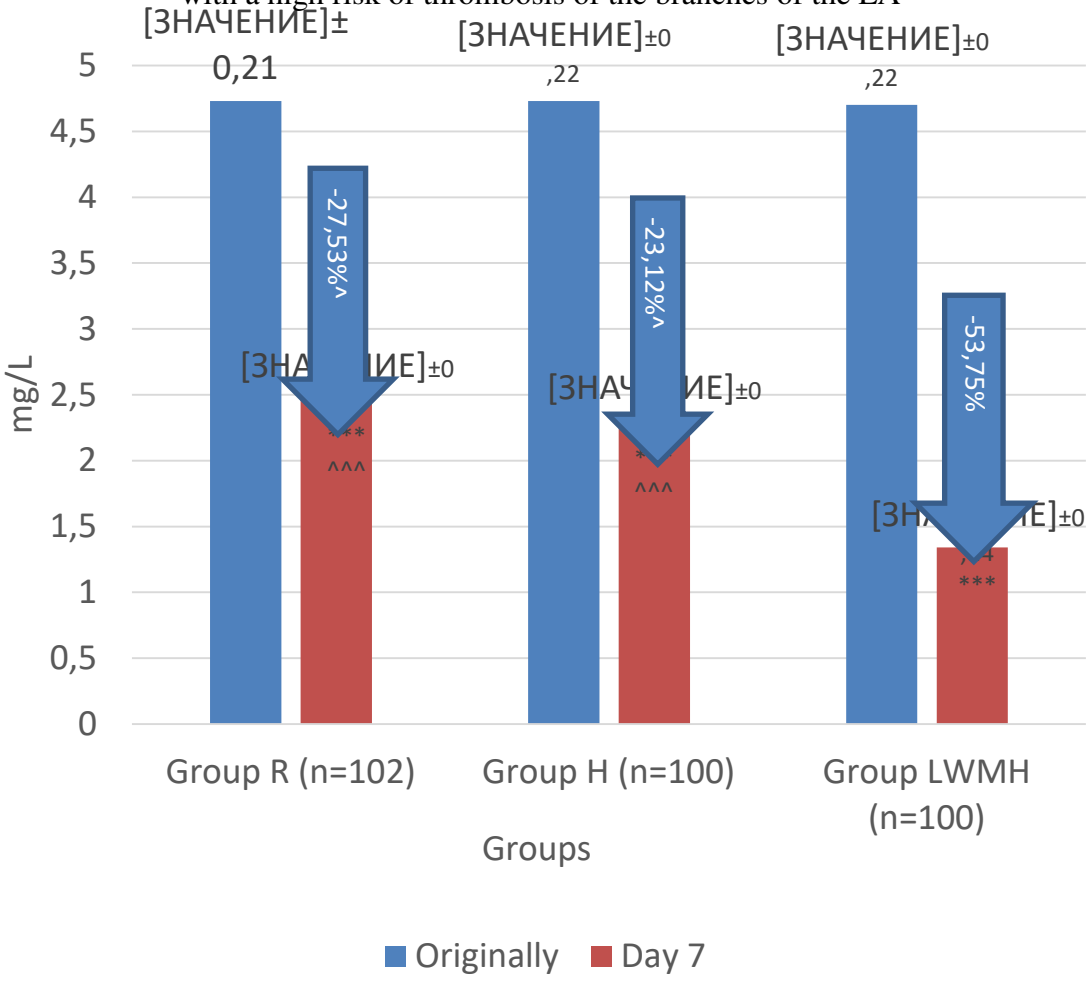
By the 7-10th day of hospitalization, a control check of the D-dimer concentration was carried out to assess the anticoagulant effect of therapy and CRP to assess the dynamics of the activity of systemic inflammation. It was revealed that in all three groups there was a significant comparable decrease in the concentration of CRP (Fig. 2). In general, the concentration of CRP decreased by 72.69% (from 51.60 ± 0.87 mg / l to 13.24 ± 0.41 mg / l, the reliability of the difference in data over time - p <0.001).



Note: * - reliability of the difference in indicators in dynamics. Three signs - p <0.001.

Analysis of the dynamics of the concentration of D-dimer in peripheral blood showed (Fig. 3) that although in all three therapeutic groups there was a significant decrease in the concentration of D-dimer (on average for all groups by 34, 75%, reliability with the initial data - p <0.001), the effect of LMWH significantly exceeded the effect of H and R (reliability of the difference in the relative dynamics in between the LMWH and R groups and the LMWH and H groups - p <0.05, the differences in the relative dynamics between the R groups and D are unreliable). As a result, at comparable initial concentrations of D dimer, by the 7th day of hospitalization in the LMWH group, a significantly lower concentration of the marker was achieved compared to groups D (p <0.001) and P (p <0.001). In groups D and R, the achieved concentration of D dimer was comparable.

Figure 3. Dynamics of the D dimer concentration in the groups of patients with COVID-19 against the background of type 2 diabetes with a high risk of thrombosis of the branches of the LA



Note: * - reliability of the difference in indicators in dynamics, ^ - reliability of the difference with the LMWH group. Three signs - p <0.001.

Thus, the study revealed significant anticoagulant efficacy of all compared treatment regimens, with a significant advantage of LMWH over H and R both in absolute and relative dynamics.

CONCLUSIONS

Patients with insufficient sensitivity to anticoagulant therapy have a higher level of glycemia (10.33 ± 0.24 mmol / L versus 9.65 ± 0.24 mmol / L, p <0.05) , a large volume of lesions of the pulmonary parenchyma (55.31 ± 1.59% versus 50.50 ± 1.60%, p <0.05) and a large diastolic diameter of the pancreas (33.45 ± 0.56 mm versus 31.56 ± 0 , 70mm, p <0.05).

The use of the developed diagnostic algorithm based on the concentration of CRP and a point risk assessment according to the instrumental scale makes it possible with a sensitivity of more than 90% to predict the development of thrombotic complications in patients with COVID-19

against the background of type 2 diabetes and to minimize the number of diagnostic procedures, including including avoiding ultrasound examination in 46.67% of patients.

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