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THE IMPORTANCE OF ANTICOAGULANT THERAPY IN THE RISK AND DEVELOPMENT OF HEMORRHAGIC STROKE IN COVID-19

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Abstract: This article analyzes the risk and development of hemorrhagic stroke during anticoagulation therapy in patients with COVID-19, as well as the effect and efficacy of different anticoagulant agents on hemorheological parameters, and the results after treatment in the early stages of the disease are presented.

Keywords: Covid-19, SARS-CoV-2, hemorrhagic stroke, activated partial thromboplastin time, D-dimer, fibrinogen, prothrombin time, heparin, enoxiparin, rivaroxaban.

Patients suffering from coronavirus infection (COVID-19) have a high risk of complications in the form of thrombosis and death, and the most appropriate type of anticoagulant drugs to use for these patients is currently becoming relevant [1,3,11]. COVID-19 patients in intensive care units (ICU) have an increased rate of venous thromboembolism (VTE), ranging from 17% to 25% [1,2,10]. Additionally, elevated D-dimer levels in patients with COVID-19 are associated with increased mortality. According to experts, timely administration of adequate anticoagulant therapy to all hospitalized patients reduces the risk of developing VTE [4,12]. At the same time, the results of many studies have shown that the use of combination anticoagulants is effective when pulmonary embolism is suspected. [5,6]. The greatest concern of increased anticoagulation use is an increased risk of bleeding in general and of intracranial hemorrhage (ICH) in particular [7,13]. Currently, oral anticoagulation is the most important risk factor for ICH and increased mortality in patients with COVID-19 at home after inpatient treatment. [8]. World studies have shown that the risk of bleeding remains high after anticoagulant measures in many patients with COVID-19 [9,15], which in turn means the relevance of our goal in our scientific research work.

The purpose of the study: To study the effectiveness of anticoagulant therapy and the risk of hemorrhagic stroke in patients with COVID-19.

Research material and method: For the study, 134 patients with a severe course of the disease of COVID-19 with a positive result of the polymer chain reaction confirming the infection of COVID-19 were selected. These patients (n=134) were conditionally divided into three groups. In the group A, n=73 (54.5%) patients who received heparin as an anticoagulant therapy at 24000-36000 ED per day for 2 weeks, n=36 (26.9%) patients in the group B received enoxiparin 1 mg/kg/day for 2 weeks, and group C consisted of n=25 (18.6%) patients received rivaroxaban 15-20 mg per day. Hemorheological parameters (D-demir, INR, fibrinogen, prothrombin time, APTT) were examined in all patients selected for the study on the day and after 10 days, early catamnesis indicators of patients, and the number and severity of hemorrhagic strokes developed in the groups were checked.

Results of the study: When analyzing the age and sex of all 62 patients in the study, the average age was 64.2±2.1, of which the proportion of men and women were 59.7% (n=37); 40.3% (n=25) respectively. According to the results of the analysis, the comorbid background is hypertension disease (HD) 62.9% (n=39), dyslipidemia 37.1% (n=23), diabetes (D) 43.5% (n=27), and ischemic heart disease (IHD) was 40.3% (n=25). (table №1).

Table 1

№	General indicators of patients				
	Indicators	Group A	Group B	Group C	Total
1	Number of patients	73 (54.5%)	36 (26.9%)	25 (18.6%)	n=134
2	Gender (men)	41 (56.2%)	23 (63.8%)	16 (64.0%)	n=80 (59.7%)
3	Comorbid conditions				
	HD	36 (49.3%)	19 (52.7%)	14 (56.0%)	n=69 (51.5%)
	Dyslipidemia	24 (31.9%)	13 (36.1%)	8 (32.0%)	n=45 (33.6%)
	D	29 (39.7%)	20 (55.5%)	9 (36.0%)	n=58 (43.3 %)
	IHD	30 (41.1%)	14 (38.9%)	10 (40.0%)	n=54 (40.3%)
4	Inflammation marker				
	C-reactive protein	58.8 ± 41.4 mg /L	61.7 ± 38.8 mg /L	55.6 ± 45.3 mg /L	57.3 ± 43.4 mg /L
5	Blood clot markers				
	D- Dimer	581.4±1.6 ng/ml	628.6±1.4 ng/ml	541.1±1.9 ng/ml	583.7±1.9 ng/ml
	Fibrinogen	7.71±1.1 µg/ml	7.42±0.9 µg/ml	7.52±1.2 µg/ml	7.55±1.2 µg/ml
	Prothrombin time	15.2±1.1 sec	14.9±1.1 sec	15.6±1.1 sec	15.2±1.1 sec
	QFTV	31.51±1.2 sec	28.2±1.7 sec	29.76±1.3 sec	29.82±1.29 sec

As a result of anticoagulant therapy, D-dimer parameters regression was found, in group A patients from 581.4±1.6 ng / ml to 334.8±2.1 ng/ml, and in group B patients from 628.6±1.4 ng / ml to 336.7±2.3 ng / ml, and in group C patients from 541.1±1.9 ng/ml to 496.6±1.4 ng/ml ($p<0.001$). Fibrin degradation product parameters regressed from 7.71±1.1 µg/ml to 3.6±1.3 µg / ml in group A patients and from 7.42±0.9 µg/ml to 3.8±1.19 µg/ml in group B patients, from 7.52±1.2 µg/ml to 3.71±1.3 µg/ml in group C patients ($p<0.005$). Prothrombin time parameters in group A patients reduced from 15.2±1.1 sec to 9.4±0.8 sec, in group B patients from 14.9±1.1 sec to 9.6±0.8 sec, and in group C patients from 15.6±1.1 sec to 9.2±0.8 sec ($p<0.001$). APTT parameters decreased from 31.51±1.29 sec to 24.16±0.8 sec in group A patients, from 28.2±1.71 sec to 26.9±1.65 sec in group B patients, and from 29.76±1.13 sec to 25.21±1.26 sec in group C patients. ($p<0.001$). (table №2).

Table 2

Intergroup changes of hemorheological parameters							
№	Hemorheological indicators	Group A: Heparin		Group B: Enoxiparin		Group C: Rivaroxaban	
		Initially	After 2 weeks	Initially	After 2 weeks	Initially	After 2 weeks
1	D-dimer	581.4 ± 1.6 ng / ml	334.8 ± 2.1 ng / ml	628.6 ± 1.4 ng / ml	336.7 ± 2.3 ng / ml	541.1 ± 1.9 ng / ml	496.6 ± 1.4 ng / ml
2	Fibrinogen	7.71 ± 1.1 μg / ml	3.6 ± 1.3 μg / ml	7.42 ± 0.9 μg / ml	3.8 ± 1.2 μg / ml	7.52 ± 1.2 μg / ml	3.71 ± 1.3 μg / ml
3	Prothrombin time	15.2 ± 1.1 sec	9.4 ± 0.8 sec	14.9 ± 1.1 sec	9.6 ± 0.8 Sec	15.6 ± 1.1 sec	9.2 ± 0.8 sec
4	APTT	31.51 ± 1.3 sec	24.16 ± 0.8 sec	28.2 ± 1.7 sec	26.9 ± 1.5 sec	29.76 ±1.3 sec	25.21±1.6 sec

The results of our study showed that among all patients (n=134) hemorrhagic stroke 2.9% (n=4) and mortality ware observed in 10.4% (n=14) due to acute respiratory distress syndrome (ARDS), the incidence of disability was 37,3% (n=50) and 49.2% (n=66) patients were discharged from the hospital with positive results (table №. 3).

Table №3

Early catamnetic results of treatment					
№		Group A	Group B	Group C	Total %
1	Hemorrhagic stroke	3 (4,1 %)	1 (2,7 %)	0 (0 %)	**n = 4 (2,9 %)**
2	Death situations (ARDS)	8 (10,9 %)	5 (13,9 %)	1 (4,0 %)	**n = 14 (10,4 %)**
3	Disability status	27 (36,9 %)	15 (41,6 %)	8 (32,0 %)	**n = 50 (37,3 %)**
4	Positive indicators	35 (47,9 %)	15 (41,6 %)	16 (64,0%)	**n = 66 (49,2 %)**

Among n=73 patients receiving heparin in group A, hemorrhagic stroke was observed in 4.1% (n=3) cases, of which 2.7% (n=2) had a subarachnoid parenchymatous form, 1.4% (n=1), hemorrhagic stroke with parenchymatous appearance was noted, and in these patients n=3 comorbid background consisted only of HD. Among n=36 patients who received enoxiparin in group B, subarachnoid hemorrhagic stroke was noted in 2.7% (n=1) cases, and the comorbid background consisted of HD and D ($p^*<0.05$). No cases of hemorrhagic stroke, i.e. ICH, were recorded among n=25 patients who received rivaroxaban..

Conclusion:

1. According to the results of the study, it was found that the percentage of hemorrhagic strokes of mixed type among patients receiving heparin was 4.1% and among patients receiving enoxiparin, the percentage of hemorrhagic stroke of subarachnoid type was equal to 2.7%.

2.Among the hemorheological indicators, all anticoagulants had a significant positive effect on fibrinogen and prothrombin time indicators, while heparin and enoxiparin agents had an effective effect on the regression of D-dimer indicator, and heparin and riboroxaban on the regression of APTT indicator.

3.In the results of the research, it was proved that riboraxaban has almost no positive effect on D-dimer while enoxiparin has almost no positive effect on APTT.

4.Heparin in the treatment of acute thromboembolic complications in sepsis-induced hypercoagulability in the acute period of COVID-19 infection, enoxiparin in the treatment of any acute thromboembolic complications against the background of hypercoagulability but sepsis is not observed, and rivaraxoban in the treatment of hypercoagulability without thromboembolic complications in COVID-19 infection.

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