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KLINIK TIBBIYOT

EKSPERIMENTAL BIOLOGIYA VA TIBBIYOT

THE EFFECTIVENESS OF ANTICOAGULANT THERAPY IN COVID-19 ASSOCIATED ISCHEMIC STROKE

Ataniyazov Makhsudjan
Khamidov Abdulakhad
Department of neurology and medical psychology
Tashkent medical academy, Uzbekistan, Tashkent

This article analyzes the effects and efficacy of various anticoagulant agents on hemorheological indicators used in Covid-19 associated ischemic stroke and post treatment results in the early stages of the disease are presented.

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

It is known that the SARS-CoV-2 virus can infect the central nervous system [1–2], and COVID-19 can cause a prothrombotic state [3]. Since the start of the SARS-CoV-2 pandemic in 2019, there has been growing evidence of neurological complications associated with COVID-19. Although SARS-Cov-2 predominantly causes acute respiratory syndrome, it can present with a variety of symptoms. Neurological symptoms, including headache, dizziness, cranial nerve injury (anosmia), cerebrovascular disease, and encephalopathy may develop alone or in parallel with respiratory distress in the early stages of COVID-19 infection [4]. The association of cerebrovascular accident with severe COVID-19 was first studied in a retrospective study conducted in China with 214 patients with COVID-19; four ischemic strokes (IS) were registered [5]. In a meta-analysis of 18 groups of studies involving 67,845 patients with COVID-19 infection, cases of ischemic stroke were registered in 1.1% of patients [3,6,8]. Increased prothrombin and activated partial thromboplastin time (APTT) in COVID-19 infection increase the risk of IS [9]. The pathophysiology of IS in COVID-19 is explained by the classical Virchow triad [7]: 1) damage by viral interactions with enzyme type 2 receptors that convert endothelium to angiotensin 2) endocytosis of the virus leads to the release of anti-inflammatory cytokines - "cytokine storm", hypercoagulation is observed 3) hyperfibrinogenemia leads to an increase in the blood coagulation system. The presence of cerebrovascular disease is a high risk factor for poor prognosis in patients with severe COVID-19. Preliminary research evidence suggests that SARS-CoV-2 infection can induce IS through viremia, hypercoagulability, endothelial dysfunction, and cardiogenic embolism associated with local and systemic immune-inflammatory processes. In this case, anticoagulant drugs in patients with COVID-19 are an important part of the treatment process.

The purpose of the study: To study the effect of various anticoagulant agents used in Covid-19 associated ischemic stroke on hemorheological parameters, as well as to analyze the results of treatment in the early stages of the disease.

Research material and methods of study: The criteria for inclusion of 62 patients selected for the study were: positive result of polymerase chain reaction confirming COVID-19 infection, the presence of signs of interstitial pneumonia on computerized tomography examination of lung tissue, confirmation of infarct-specific symptoms in brain tissue by computerized tomography examination, and the presence of clinical signs specific to COVID-19 infection was considered.These patients (n = 62) were conditionally divided into three groups. In the group A, n = 33 (53.12%) patients who received heparin as an anticoagulant therapy at 24000-36000 ED per day for 2 weeks, n = 17 (27.4%) patients in the group B received enoxiparin 1 mg / kg / day for 2 weeks, and group C consisted of n = 12 (19.4%) 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 2 weeks after application and monitored for 1 month.

The 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. 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 1).

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 ± 1.19 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 ± 1.29 sec	24.16 ± 0.8 sec	28.2 ± 1.71 sec	26.9 ± 1.65 sec	29.76 ±1.13 sec	25.21±1.26 sec

The table shows that when we compared with pre-treatment hemorheological parameters after 2 weeks, the following percentages decreased in groups A, B, and C: D-dimer 42.4%; 46.4%; 8.2%; respectively ($p<0.001$), fibrin degradation products 53.3%; 48.8%; 50.7%; respectively ($p<0.001$), prothrombin time 38.1%; 35.6%; 41.1%; respectively ($p<0.001$), APTT 23.3%; 4.6%; 15.3%; respectively ($p<0.001$). (Table 2).

Percentage changes in hemorheological indicators in groups				
№	Hemorheological indicators	Group A: Heparin	Group B: Enoxiparin	Group C: Rivaroxaban
1	D-dimer	42.40%	46.40%	8.20%
2	Fibrinogen	53.30%	48.80%	50.70%
3	Prothrombin time	38.10%	35.60%	41.10%
4	APTT	23.30%	4.60%	15.30%

The results of our study showed that among all patients (n = 62) mortality was observed in 22.5% (n = 14) due to acute respiratory distress syndrome (ARDS), the incidence of disability was

45.2% (n = 28) and 32.3% (n = 20) patients were discharged from the hospital with positive results (Table 3).

Early catamnestic outcomes of treatment			
№		Number	percentage
1	Deaths (ARDS)	14	22.5%
2	Disability status	28	45.2%
3	Positive indicators	20	32.3%

Conclusion: Among the hemorheological indicators, all anticoagulants have a significant positive effect on fibrinogen and prothrombin time, heparin and enoxyparin are effective against D-dimer, heparin and riboraxaban are effective against APTT. However, riboraxaban has almost no positive effect on D-dimer while enoxiparin has almost no positive effect on APTT. 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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