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The Analysis of Long-Term Results and Quality of Life in Patients with Massive Pulmonary Embolism in the Course of Treatment with Thrombolytic and Anticoagulant Drugs

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RELEVANCE Chronic post-embolic pulmonary hypertension (CPEPH) is a complication of pulmonary thromboembolism found almost in every 10th patient. A special risk group consists of patients with a moderately high risk of pulmonary embolism associated death according to stratification of the probability of early death of the European Society of Cardiology. The development of this condition is potentially preventable with timely and adequate therapy in these patients. We have improved the approach to the treatment of pulmonary embolism patients, which allows indications for thrombolytic therapy to be clarified and expanded. The aim of the study is to evaluate its effectiveness in the long-term period, as well as analyze the qualities of life of patients with massive pulmonary embolism, who underwent thrombolytic and anticoagulant therapy.

MATERIAL AND METHODS The treatment, as well as the analysis of long-term results and quality of life of 71 patients aged 29 to 88 years with diagnosed pulmonary embolism with a moderately high risk of early death were performed. All patients underwent general clinical and biochemical blood tests, D-dimer, ECG, echocardiography, ultrasound of the lower extremities veins, CT angiopulmonography. We registered the dynamics of echocardiographic symptoms of the right heart overload over 6 months (right ventricle size, pulmonary hypertension, the degree of tricuspid regurgitation), and assessed the quality of life based on a survey with the establishment of the appearance of shortness of breath, tachycardia, hospitalizations for heart failure during the study period.

Depending on the type of therapy, the patients were divided into two groups: 38 patients with thrombolytic therapy and 33 patients with anticoagulant therapy. Subsequently, their comparative analysis was carried out.

RESULTS AND CONCLUSION In patients with pulmonary embolism of moderately high risk of early death, who underwent thrombolytic therapy, chronic post-embolic pulmonary hypertension developed 2.9 times less and a higher quality of life retained in these patients than in patients treated with anticoagulant drugs.

Keywords: pulmonary embolism, anticoagulant therapy, thrombolytic therapy, chronic post-embolic pulmonary hypertension

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ACT — anticoagulant therapy
CT — computed tomography
CPEPH — chronic post-embolic oulmonary hypertension
ECG — electrocardiography
EchoCG — echocardiography
INR — international normalized ratio
PE — pulmonary embolism
TLT — thrombolytic therapy

INTRODUCTION

Chronic post-embolic pulmonary hypertension (CPEPH) is a progressive disease with the development of chronic pulmonary heart with a gradual increase of right heart chambers dilation, growth of heart failure in patients who have undergone pulmonary embolism (PE) [1, 2].

The incidence of CPEPH reaches 8.8% in patients undergoing pulmonary embolism, significantly reducing the quality and life expectancy of these patients. The average life expectancy in patients with CPEPH is 2.8 years from the date of diagnosis [3-5].

The most important predisposing factors for the development of CPEPH in patients with pulmonary embolism are the inadequate volume and timing of initiation of therapy, which leads to a lack of complete recanalization of the pulmonary vessels with a change in the lumen and the development of pulmonary hypertension with an average pressure in the pulmonary artery above 30 mmHg [6].

CPEPH most often develops in patients with a moderate-high risk of pulmonary embolism associated with death, according to the stratification of the risk of early death of the European Society of Cardiology 2014 [6, 7]. This is due to the fact that these patients have a rather massive lesion of the pulmonary bed, and clinical symptoms may not be expressed, which leads to the late treatment of such patients for medical help. Also, in these patients, the volume of optimal therapy is not clearly defined. In patients with a moderate-high risk of pulmonary embolism associated with death, it is possible to carry out both thrombolytic (TLT) and anticoagulant (ACT) therapy, while there is no clear indication in which particular case and what kind of therapy should be preferred [8, 9]. As a result, up to 15% of patients with a moderate to high risk of death from pulmonary embolism do not receive the necessary amount of therapy [10].

In N.I. Pirogov NMSC a scale for choosing the optimal volume of therapy was developed in order to optimize the treatment tactics for patients with pulmonary embolism (Table 1) [11].

Table 1

The scale for determining the management of patients with pulmonary embolism

Criteria	Score
Hypotension less than 90/60 mm Hg	5
The size of the right ventricle is larger than the left	4
The paradoxical movement of the interventricular septum	3
Right ventricular hypokinesia	3
Elevated Troponin values	3
Dilation of the right ventricle of more than 3 cm according to echocardiography, but not exceeding the size of the left ventricle	2
Deep $S_I Q_{III}$ on ECG	2
Pre- or syncopal state	2
Increased NT - proBNP values not more than 3,000 pmol/ml	1
Lesion of 10 or more segmental arteries	1
Increased pressure in the pulmonary artery more than 50 mm Hg	1
Dilated inferior vena cava, more than 20 mm by echocardiography	1
One or more of the following symptoms: tachycardia with a heart rate of more than 100 beats per minute due to pulmonary embolism; hypoxemia with arterial blood saturation less than 90%; jugular venous distention, loud second heart sound over the pulmonary artery.	1 (regardless of the number)
The choice of therapy (according to the sum of points): Thrombolytic (5 or more); Anticoagulant (less than 5).	

The suggested scale expands and refines the indications for TLT in patients with a moderately high risk of early death from pulmonary embolism [11].

MATERIAL AND METHODS

We conducted a retrospective study (71 patients) who were hospitalized with pulmonary embolism of moderately high risk of early death, confirmed by CT angiography. In all patients, the diagnosis was verified on the first day. The distribution according to the level of proximal occlusion was as follows: the main pulmonary arteries - 8%, lobar - 68%, segmental arteries - 51%.

All patients, according to the scale developed by the NMSC for selecting the optimal volume of therapy, had indications for TLT. However, the suggested scale currently does not have a sufficient degree of convincing evidence. Therefore, the choice of therapy was based on the generally recognized stratification of the risk of early death of the European Society of Cardiology from 2014.

Patients who underwent TLT with Actilyse at a dose of 100 mg according to the indications of stratification of the risk of early death of the European Society of Cardiology from 2014 and according to the proposed criteria, made up the Group 1 — 38 patients. There were 16 men and 22 women. The age ranged from 29 to 82 years, the mean age was 55.4±15.1 years.

Patients of the second (control) group, who, according to the scale developed at the NMSC, could have undergone TLT, but according to indications of a stratification of the risk of early death of the European Society of Cardiology from 2014, TLT was not recommended, so they underwent ACT:switch to warfarin under the control of the international normalized ratio (INR).

2. Low molecular weight heparin (fraxiparin in therapeutic dosage), followed by switching to warfarin under the control of INR.
3. Rivaroxaban 30 mg per day for 3 weeks, with the recommendation of the subsequent transfer of patients to a dose of 20 mg per day.
4. Apixaban 10 mg 2 times during the first 7 days, then 5 mg 2 times a day.

Since the efficacy of all types of anticoagulant therapy is almost the same, all these patients are combined into one group — 33 patients. There were 15 men and 18 women. The age of the patients ranged from 24 to 88 years, the mean age was 53.7 ± 17.4 years.

All patients underwent general clinical and biochemical blood tests, *D*-dimer study, electrocardiography (ECG), echocardiography (EchoCG), ultrasound dopplerography of the lower extremities veins, computed tomographic angiopulmonography . After 6 months, Echocardiography was monitored for signs of an increase in overload of the right heart (sizes of the right ventricle, pulmonary hypertension, degree of tricuspid regurgitation), and the quality of life was assessed based on a survey with the establishment of shortness of breath, tachycardia, and the frequency of hospitalizations for heart failure during the study period .

Statistical analysis was performed using the computer program *"Statistica 6.0"*. Data are presented as mean values with standard deviations. To assess the statistical differences, paired *t*- test of Student and Mann – Whitney were used. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

After TLT and ACT, all patients with pulmonary embolism were prescribed anticoagulant drugs at the outpatient stage of treatment. However, these recommendations were not always implemented by patients. It was found that regardless of the type of therapy, when prophylactic anticoagulant drugs were canceled after discharge from the hospital for up to 6 months, 11.3% (8 out of 71) patients developed recurrence of deep vein thrombosis of the lower extremities, and 37.5% (3 of 8) diagnosed with repeated pulmonary embolism.

When studying the results of treatment and the quality of life of patients with massive pulmonary embolism, after 6 months, it was found that among patients with TLT, signs of CPEPH developed in 4 patients (10.5%), and among patients who were on ACT — in 10 (30.3%) (p=0.04). All patients who developed CPEPH did not seek medical help on the first day of the disease. On average, they started treatment on days 9–14 in the group of patients with massive pulmonary embolism and performed TLT, and on days 7–14 in the group with ACT.

Patients with massive pulmonary embolism and performed TLT and ACT who developed signs of CPEPH were at a moderate risk of pulmonary embolism, according to the risk stratification of the European Society of Cardiology. The average volume of pulmonary lesion in the total absence of blood flow in the segmental arteries of the lungs was comparable and amounted to 11.6±0.4 and 11.4±1.1 segmental arteries, and the regression during therapy was negligible: 9.8±0.7 and 10.5±0.2 segmental arteries, respectively.

Table 2

Echocardiography criteria for overloading the right heart in the long-term treatment with ACT and TLT

Indicator	Group of patients		
	TLT (n=38)	ACT (n=33)	R
Dimensions of the right ventricle upon admission to the hospital	3.1±0.7 cm	3.3±0.4 cm	0.15
Dimensions of the right ventricle upon discharge from the hospital	2.6±0.5 cm	3.2 ± 0.4 cm	<0.01
Dimensions of the right ventricle over 6 months	2.9±0.6 cm	3.3±0.8 cm	0.02
Dilation of the right atrium over 65 ml upon admission	52.6%	45.5%	0.64
Dilation of the right atrium of more than 65 ml upon discharge from the hospital	31.6%	36.4%	0.8
Dilation of the right atrium over 65 ml over 6 months	31.6%	36.4%	0.8
Mean pulmonary pressure upon admission to hospital	44.9±15.2 mmHg	42.2±17.1 mmHg	0.48
Mean pressure in the pulmonary artery upon discharge from the hospital	28.5±10.3 mmHg	37.3±19.6 mmHg	0.02
Mean pressure in the pulmonary artery over 6 months	29.1±7.3 mmHg	41.2±11.7 mmHg	<0.01
Tricuspid regurgitation ≥2 upon admission to the hospital	39.5%	42.4%	0.81
Tricuspid regurgitation ≥2 upon discharge from the hospital	21%	33.3%	0.29
Tricuspid regurgitation ≥2 in 6 months	21%	33.3%	0.29
Indicator	Group of patients		
	TLT (n=38)	ACT (n=33)	R
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Tricuspid regurgitation ≥2 in 6 months	21%	33.3%	0.29

Note: ACT — anticoagulant therapy; TLT — thrombolytic therapy

Compared to a group of patients with pulmonary embolism which was carried ACT, dimensions of the right ventricle were significantly decreased by the time of discharge (p<0.01) and remained statistically significantly smaller upon examination after 6 months (p=0.02). The same dynamics was observed when comparing the average pressure in the pulmonary artery upon discharge from the hospital and 6 months later, p=0.02 and p <0.01, respectively. In the group of patients with pulmonary embolism treated with anticoagulant drugs, there was a greater increase in these indicators than in patients who underwent TLT.

Patients with developed CPEPH after discharge from the hospital evaluated their health status higher than after 6 months. They explained the deterioration of the condition by the appearance of shortness of breath and tachycardia during physical activity associated with the presence of pulmonary hypertension. Moreover, the higher the degree of pulmonary hypertension, the more patients were limited in physical activity, which led to a decrease in the quality of their life.

Another component that worsens the quality of life of patients with massive pulmonary embolism who developed post-embolic pulmonary hypertension was an increase in requests for outpatient and inpatient care for manifestations of heart failure.

In 2 patients (6%) undergoing massive pulmonary embolism who were treated with ACT paroxysmal atrial fibrillation appeared.

FINDINGS

1. In patients with massive pulmonary embolism who received thrombolytic therapy, symptoms of chronic post-embolic pulmonary hypertension, which reduce the duration and quality of life, developed 2.9 times less than in patients receiving anticoagulant drugs, respectively, 30.3% and 10.5% of cases (p=0.04).

2. In the group of patients with pulmonary embolism treated with anticoagulant drugs, there was a more pronounced increase in the size of the right ventricle and the average pressure in the pulmonary artery 6 months after discharge from the hospital, p<0.01 and p=0.02, respectively.

3. Regardless of the type of therapy for patients with pulmonary embolism, when drug therapy was discontinued at the outpatient stage, deep vein thrombosis of the lower extremities developed in 11.3%, and relapse of pulmonary embolism developed in 4.2%.

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