

Thrombolytic and Anticoagulant Therapy for Pulmonary Embolism with High and Intermediate Risk of Early Death. Part 3. An Effect on Pulmonary Perfusion with High and Intermediate Risk of Early Death

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BACKGROUND The advantage of thrombolytic therapy (TLT) over anticoagulant therapy (ACT) in patients with a high risk of early death (hemodynamic disorders) in acute pulmonary embolism is considered proven. But the advantage of thrombolytic therapy over anticoagulant therapy remains uncertain in patients with an intermediate risk. Perfusion lung scintigraphy helps provide a quantitative comparison of changes in pulmonary blood flow with the use of different treatment methods in subgroups of high and intermediate risk of an adverse outcome.

THE AIM OF STUDY is to compare the effectiveness of thrombolytic and anticoagulant therapy in the treatment of acute pulmonary embolism in patients with a high and intermediate risk of early death in terms of the dynamics of pulmonary perfusion disorders.

STUDY DESIGN: a prospective non-randomized study. The introduction of a thrombolytic was considered as intervention. The comparison group consisted of patients who received an anticoagulant. Thrombolysis in patients with intermediate risk was indicated in the absence of a potential threat of hemorrhagic complications, a deficit of pulmonary perfusion above 40%, a high level of pulmonary hypertension and a high probability of cardiac decompensation. The method of comparison was the quantitative result of pulmonary perfusion deficiency.

DESCRIPTION OF THE METHOD Radionuclide and CT studies were carried out using a hybrid system SPECT/CT Discovery NM/CT 670 (GE, USA): the perfusion was evaluated with 80–120 MBq of ^{99m}Tc macrotech radiopharmaceutical (RP) (effective equivalent dose of 0.8–1.3 mSv), CT angiography was performed with 70–100 ml of radiopaque substance Visipaque (effective equivalent dose of irradiation 9.4–10.3 mSv). The accumulation deficit of an area equal to a segment was counted as a perfusion deficiency of 5% (subsegmental 2.5%), inferior lobe – 25%, an area equal to the right lung – 55%, the left lung – 45%.

CHARACTERISTICS OF THE SAMPLE In a sample of 503 patients who received treatment at the Intensive Care Unit for Surgical Patients of the N.V. Sklifosovsky Institute for Emergency Medicine from 2011 to 2016, the overall mortality rate was 14.7% (95% CI 11.7; 18.1) (74/503); anticoagulation therapy – 17.8% (95% CI 13.5; 22.8) (50/281); thrombolytic therapy – 10.8% (95% CI 7.1; 15.6) (24/222); $p=0.031$, Fisher's test, $P=0.60$. At a high risk of death, the mortality rate in the thrombolytic therapy group was 30.2% (19/63) versus 47.1% (32/68) in the anticoagulant therapy group; $p=0.051$, the Fisher's test; $P=0.51$. At an intermediate risk, it was 3.2% (5/158) and 8.4% (8/214); $p=0.049$, the Fisher's test, $P=0.54$.

Changes in pulmonary perfusion deficiency as a result of treatment were performed in 169 patients who promptly underwent a primary and repeated dynamic scintigraphic study: 127 patients after thrombolysis (of which 38 patients had a high risk and 88 had an intermediate risk) and 42 patients who were treated with an anticoagulant (5 – high risk, 37 – intermediate risk). The groups did not differ in age and gender composition: the mean age was 59±16; Me 61 (49; 71) and 57±14 years; Me 58 (43; 67), respectively; $p=0.50$ (Mann–Whitney test); men/women: 50/77 and 12/30; $p=0.27$, the Fisher's test. The groups differed in the presence of cancer: in the ACT group, the proportion of patients with cancer was 21.4% (9/42), and in the TLT group it was 4.7% (6/127), $p=0.003$, the Fisher's test, $P=0.85$.

RESULTS Patients of high and intermediate risk, who received thrombolysis, were in a significantly more serious condition in terms of baseline characteristics. Both methods of treatment were effective. In high-risk patients, perfusion deficiency regressed: from 57±10% (Me 60 (50; 65)) to 31±15% (Me 30 (20; 40)), $p<0.00001$ (Wilcoxon test), $Es=2.08$, $P=1.00$ after TLT; from 38±9% (Me 40 (35; 40)) to 14±8% (Me 10 (10; 20)), $p=0.043$ (Wilcoxon test), $Es=2.72$, $P=0.93$ after ACT. In patients with intermediate risk, perfusion deficiency regressed: from 48±9% (Me 50 (40, 55)) to 24±13% (Me 20 (15; 30)), $p<0.00001$ (Wilcoxon test) after TLT; from 38±11% (Me 40 (30; 45)) to 24±15% (Me 15 (15; 30)), $p=0.00003$ (Wilcoxon test) after ACT. The effect size for TLT was $Es=2.16$, for ACT $Es=1.13$. The power of the study was $P=1.00$ and $P=0.99$.

CONCLUSION Thrombolytic therapy was more effective in restoring pulmonary perfusion compared to anticoagulants in patients with an intermediate risk of early death: the effect of thrombolysis was greater than that of anticoagulant therapy ($Es=2.16$ and $Es=1.13$).

The absence of the effect of restoring pulmonary perfusion during thrombolysis was noted less frequently compared to the results of anticoagulant therapy: in 5.5% (95% CI 2.2–11.0) vs. 19.0% (95% CI 8.6–34.1).

Key words: pulmonary embolism, thrombolytic therapy, anticoagulant therapy, perfusion scintigraphy, pulmonary perfusion deficiency, pulmonary hypertension, intermediate risk of early death

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ACT — anticoagulant therapy

CI — confidence interval

PE — pulmonary embolism

SPECT/CT angiography — single photon emission computed tomography with computed tomography angiography

TLT — thrombolytic therapy

The advantage of thrombolytic therapy (TLT) over anticoagulant therapy (ACT) in patients with high risk of death (hemodynamic disorders) due to acute pulmonary embolism is considered proven and reflected in domestic and foreign recommendations for the treatment of pulmonary embolism (PE) [1–5]. At the same time, there are facts of insufficient use of TLT even in patients with a high risk of death. Indicative data given by P.D. Stein (2012) for all unstable patients with pulmonary embolism in the United States from 1999 to 2008: out of 72,230 people, only 21,390 (30%) received TLT, while mortality was 15% (3,105 out of 21,390) against 47% (23,820 out of 50,840) without TLT ($P < 0.0001$) [6].

The advantages of thrombolytic treatment remain uncertain for intermediate risk patients. The apparent decrease in mortality, rapid stabilization of hemodynamics and improvement in oxygenation are associated, according to representative meta-analyses, with a slight increase in the risk of life-threatening hemorrhagic complications [7–15]. The authors of the Cochrane Collaboration meta-analysis of 2015, formulating recommendations for further research based on generalized results, note the importance of stratification of hemodynamically stable and unstable patients [16].

Perfusion lung scintigraphy, being one of the main methods for assessing perfusion deficiency (especially with subsegmental location of an embolus), makes it possible to perform quantitative comparison of changes in pulmonary blood flow using different methods of treatment in subgroups of high and intermediate risk of adverse outcome.

The aim of study is to compare the efficacy of TLT and ACT in the treatment of acute pulmonary embolism in patients with high and intermediate risk of early death according to the dynamics of impaired pulmonary perfusion.

Study design: A prospective, non-randomized study. The intervention was the introduction of a thrombolytic drug. The comparison group consisted of patients who received an anticoagulant. The comparison method is a quantitative result of a deficiency of pulmonary perfusion, obtained during perfusion scintigraphy in subgroups of high and intermediate risk of early death in acute pulmonary embolism.

The determination of the risk of adverse outcome was carried out according to the following criteria. The high risk was attributed to patients with signs of systemic hemodynamic disorders: systolic blood pressure below 90 mm Hg upon admission and/or at the prehospital stage in cases where hypotension was recorded in ambulance cards. The high-risk group also included patients who experienced vascular collapse with a short-term loss of consciousness, falling from an orthostatic position to a horizontal position in the next few hours before hospitalization together with sudden suffocation and severe weakness.

Hemodynamically stable patients with elevated levels of troponin in the blood, signs of dilatation of the right ventricle during an echocardiographic study and/or with a PESI (Pulmonary Embolism Severity Index) score higher than 85 were considered as intermediate risk patients. Among them are patients with acute disorders of the heart rhythm, tachycardia over 120 beats/min and systolic pressure above 90 mm Hg. [2].

Thrombolytic therapy in patients with intermediate risk was prescribed in the absence of a potential threat of hemorrhagic complications, a lack of pulmonary perfusion more than 40%, a high level of pulmonary hypertension and a high probability of cardiac decompensation. If there are signs of unstable hemodynamics, a contraindication for the appointment of thrombolysis was an increased risk of bleeding [1–4].

Inclusion criteria: age over 15 years; verified diagnosis of PE by perfusion scintigraphy and hybrid single-photon emission computed tomography (SPECT/CT scan) of the lungs with intravenous bolus contrast enhancement; high and intermediate risk of early death [2].

Exclusion criteria were negative or questionable pulmonary scan, low risk of adverse outcome.

METHOD DESCRIPTION

Radionuclide and CT studies were carried out on the hybrid system SPECT/CT “Discovery NM / CT 670” (GE, USA): perfusion was estimated from 80–120 MBq of the ^{99m}Tc -macrotech radiopharmaceutical (effective equivalent radiation dose is 0.8–1.3 mSv), CT angiography was performed with 70–100 ml of the Visipaque radiopaque substance (effective equivalent radiation dose is 9.4–10.3 mSv). The total radiation exposure in a hybrid study with SPECT/CT angiography of the lungs was 10.2–11.6 mSv. A typical scintigraphic sign of pulmonary embolism is an edge triangular (wedge-shaped) perfusion defect with a base facing the pleura, repeated in all standard projections and indicating the absence of regional pulmonary blood flow. As a rule, several segmental and subsegmental edge defects or a combination of lobar and segmental/subsegmental defects are visualized on scintigrams. To determine the total deficit of perfusion, each accumulation defect with an area equal to a segment is taken for a perfusion

deficit of 5% (subsegmental – 2.5%); an area equal to the lower lobe – 25%; an area equal to the right lung – 55%; left lung – 45% [17].

Statistical data processing was performed using the STATISTICA, StatSoft Inc. software package (USA). The normality of distributions was assessed by the Shapiro-Wilk test (all distributions did not meet the criterion of normality). Estimates of central trends and variations are presented by means of standard deviations $M \pm SD$ and medians with quartile range Me (1st quartile, 3rd quartile).

For quantitative comparisons, nonparametric rank tests were used: the Mann-Whitney test for independent groups, the Wilcoxon test for intragroup dynamic comparisons. Percentage comparisons were performed using Fisher's two-sided test. For equity estimates, a 95% confidence interval was calculated (95% CI). The exact values of the significance level of the identified differences p for each comparison are presented in the text and tables. The threshold value was considered $p \leq 0.05$ (error control type I). To control the error of the second type, the power of research P was calculated; threshold value $P \geq 0.8$ for $\alpha = 0.05$. To assess the strength of differences, the standardized effect (Es) was calculated using the formula $M1 - M2 / (SD1 + SD2) / 2$. The estimated strength of the effect according to Cohen (1983) is as follows: $Es = 0.20$ is a small effect, $Es = 0.50$ is an average effect, $Es = 0.80$ is a strong effect [18].

Description of the sample. In a sample of 503 people, the diagnosis of “pulmonary embolism” was verified by perfusion scintigraphy in 381 patients who were treated in the intensive care unit and intensive care for surgical patients of the N.V. Sklifosovsky Research Institute from 2011 to 2016.

The overall mortality for the entire sample was 14.7% (95% CI 11.7; 18.1) (74/503); including patients with ACT – 17.8% (95% CI 13.5; 22.8) (50/281); TLT – 10.8% (95% CI 7.1; 15.6) (24/222); $p = 0.031$, Fisher criterion, $P = 0.60$.

The mortality in the TLT group with high risk of death was 30.2% (19/63) versus 47.1% (32/68) in the ACT group; $p = 0.051$, Fisher criteria; $P = 0.51$. At an intermediate risk of early death, it was 3.2% (5/158) and 8.4% (8/214); $p = 0.049$, Fisher test, $P = 0.54$.

The incidence of major complications during TLT and ACT in patients with high and intermediate risk of early death are presented in Table 1. In both subgroups (high and intermediate risk) thrombolytic and anticoagulant treatment methods did not differ in the incidence of hemorrhagic complications, both clinically significant, including cranial bleeding, and minor episodes. In patients at high risk of early death, thrombolysis was associated with a higher rate of hospital recurrence of pulmonary embolism compared with anticoagulant use (27.0% vs. 11.8%, $p = 0.044$, Fisher test, $P = 0.60$), in contrast to patients with intermediate risk, who had no such differences (10.7 and 11.7%, $p = 0.869$, Fisher test, $P = 0.05$). In patients with an intermediate risk of early death, pulmonary infarction after thrombolysis developed less frequently as compared with the results of treatment with an anticoagulant: in 17.6% versus 30.0%, $p = 0.007$, Fisher test, $P = 0.41$.

Table 1

The incidence of basic complications development in patients with high and intermediate risk of early death after thrombolytic and anticoagulant therapy

	Thrombolytic therapy n=222		Anticoagulant therapy n=281		Fisher's test	P, power
High risk						
	n=63		n=68			
Mortality rate	19/63	30.2%	32/68	47.1%	0.051	0.51
Major hemorrhages	2/63	3.2%	4/68	5.9%	0.682	0.11
Minor hemorrhages	6/63	9.5%	3/68	4.4%	0.311	0.21
Cranial hemorrhages	0/63	0%	1/68	1.5%	1.00	0.15
Hospital re-occurrence of pulmonary embolism	17/63	27.0%	8/68	11.8%	0.044	0.60
Pulmonary infarction	16/63	25.4%	17/68	25.0%	1.00	0.05
Acute disorders of heart rhythm	8/63	12.7%	8/68	11.8%	1.00	0.05
Intermediate risk						
	n=159		n=213			
Mortality rate	5/159	3.1%	18/213	8.5%	0.049	0.58
Major hemorrhages	4/159	2.5%	5/213	2.3%	1.00	0.05
Minor hemorrhages	5/159	3.1%	17/213	9.0%	0.074	0.28
Cranial hemorrhages	2/159	1.3%	1/213	0.5%	0.578	0.08
Hospital re-occurrence of pulmonary embolism	17/159	10.7%	25/213	11.7%	0.869	0.05
Pulmonary infarction	28/159	17.6%	64/213	30.0%	0.007	0.41
Acute disorders of heart rhythm	14/159	8.8%	17/213	8.0%	0.850	0.05

The comparison of the efficacy of two methods of treatment in the high and intermediate risk groups of early death in terms of the dynamics of pulmonary perfusion deficiency was performed in 169 people who underwent a primary and repeated dynamic scintigraphic study: in 127 patients after thrombolysis and in 42 who were treated with an anticoagulant. The groups did not differ in age and gender composition: average age 59 ± 16 ; Me 61 (49; 71) and 57 ± 14 years; Me 58 (43; 67), respectively; $p = 0.50$ Mann-Whitney test; men/women: 50/77 and 12/30; $p = 0.27$, Fisher test. The groups differed in the presence of cancer: in the ACT group, the proportion of patients with cancer was 21.4% (9/42), and in the TLT group it was 4.7% (6/127), $p = 0.003$, Fisher test, $P = 0.85$ (Table 2).

Table 2

The comparison of anthropometric and clinical data of groups

	Thrombolytic therapy n=127	Anticoagulant therapy n=42	P, Fisher's test	P, power
Age	59±16; Me 61 (49;71)	57±14; Me 58 (43; 67)	0.496 Mann-Whitney test	0.12
Gender male\female	50\77	12\30	0.268	0.23
Bone trauma	11	0	0.067	0.51
Major surgery	6	5	0.143	0.40
Cancer	6	9	0.003	0.85
Diabetes	7	2	1.00	0.05
Initial rhythm disturbances not associated with PE	14	6	0.586	0.10

In the TLT group, 39 people were in the high-risk subgroup, 88 were in the intermediate-risk subgroup. In the ACT group, 5 were in the high-risk subgroup, and 37 were in the intermediate-risk subgroup.

Unfractionated heparin was injected into the peripheral vein through the infuser at a dose of from 1.0 to 1.7 thousand units/h with a switch to the anticoagulant of indirect action, warfarin, by day 3-5. The thrombolytic was administered through the infuser into the peripheral vein; of 127 patients presented, alteplase was used in 95 cases, urokinase in 24 cases and streptokinase in 8 cases. A full dose of thrombolytic agent was used.

RESULTS

To compare the efficacy of TLT and ACT with different risk of adverse outcome, the dynamics of changes in the percentage of pulmonary perfusion deficit and the number of affected pulmonary segments before and after treatment were analyzed. The baseline assessment in all patients was performed on the day of admission. The dynamics was evaluated on the following day after administration of a thrombolytic and on day 4–5 after initiating ACT. A preliminary analysis of these parameters in the ACT group one day after the initiation (by analogy with TLT) did not reveal any statistically significant differences compared with the initial data.

The dynamics of indicators of pulmonary perfusion deficiency in the subgroup of high risk of early death during TLT and ACT are presented in Table 3 and Fig. 1. Both methods of treatment were effective, the perfusion deficit was statistically significantly reduced: with TLT from $57\pm 10\%$ (Me 60 (50; 65)) to $31\pm 15\%$ (Me 30 (20; 40)), $p<0.00001$ Wilcoxon test, $P=1.00$; with ACT from $38\pm 9\%$ (Me 40 (35; 40)) to $14\pm 8\%$ (Me 10 (1;20)), $p=0.043$, Wilcoxon test, $P=0.93$.

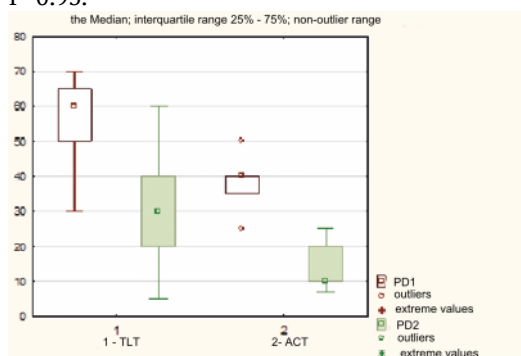


Fig. 1. The dynamics of pulmonary perfusion deficiency after thrombolytic and anticoagulant therapy in the subgroup of high risk of early death.

Notes: PD1 — initial perfusion deficiency; PD2 — changed index of perfusion deficiency as a result of the treatment; ACT — anticoagulant therapy; TLT — thrombolytic therapy

In the TLT group, the initial perfusion deficit was statistically significantly higher compared with the ACT group and was therefore $57\pm 10\%$; Me 60 (50; 65) vs. $38\pm 9\%$; Me 40 (35; 40); $p=0.001$, Mann-Whitney test. However, the strength of the effect was high for both methods of treatment: $Es=2.08$ and $Es=2.72$. The second indicator $Es=2.72$ (for ACT) can most likely be considered overstated due to the small number of observations. However, the power was high for both groups: $P=1.00$ and 0.93 , respectively.

Table 3

The dynamics of pulmonary perfusion deficiency in patients with a high-risk of early death after thrombolytic and anticoagulant therapy

	Studied indicators	Baselines	Dynamics as a result of treatment	p Wilcoxon test	Es	P
Thrombolytic therapy n=39	Pulmonary perfusion deficiency, %	57 ± 10 Me 60 (50; 65)	31 ± 15 Me 30 (20; 40)	<0.00001	2.08	1.00

	Number of affected segments	12±2 Me 12 (10; 14)	7±4 Me 6 (4; 9)	0.00003	1.76	1.00
Anticoagulant therapy n=5	Pulmonary perfusion deficiency, %	38±9 Me 40 (35; 40)	14±8 Me 10 (10; 20)	0.043	2.72	0.93
	Number of affected segments	9±1 Me 9 (8; 10)	5±3 Me 5(3; 6)	0.068	2.25	0.60
Mann-Whitney test		0,001 0.023	0.013 0.333			

In patients with an intermediate risk of early death, the initial perfusion deficit was also statistically significantly different and was higher in patients with thrombolytics treatment: 48±9% (Me 50 (40; 55)) versus 38±11% (Me 40 (30; 45)), $p=0.00006$, Mann-Whitney test, $P=1.00$. With both methods of treatment, the perfusion deficit decreased, and the differences were recorded at a high level of statistical significance: in the TLT from 48±9% (Me 50 (40; 55)) to 24±13% (Me 20 (15; 30)), $p<0.00001$, Wilcoxon test; in the ACT group from 38 ±11% (Me 40 (30; 45)) to 24±15% (Me 15 (15; 30)), $p=0.00003$, Wilcoxon test (Table 4, Fig. 2). However, the strength of the effect in TLT was almost twice as high compared with the results of the ACT, $Es=2.16$ and 1.13. The power of comparisons was 1.00 and 0.99 respectively.

Table 4

The dynamics of pulmonary perfusion deficiency after thrombolytic and anticoagulant therapy in the subgroup of intermediate risk of early death

	Studied indicators	Baselines	Dynamics as a result of treatment	p, Wilcoxon test	Es	P
TLT n=88	Pulmonary perfusion deficiency, %	48±9 Me 50 (40; 55)	24±13 Me 20 (15; 30)	<0.00001	2.16	1.00
	Number of affected segments	10±2 Me 10 (9; 12)	5±3 Me 5 (4; 8)	<0.00001	2.00	1.00
ACT n=37	Pulmonary perfusion deficiency, %	38±11 Me 40 (30; 45)	24±15 Me 15 (15; 30)	0.00003	1.13	0.99
	Number of affected segments	9±2 Me 9 (8; 10)	6±3 Me 6 (4; 9)	0.002	0.89	0.99
Mann-Whitney test		0.00006 0.003	0.94 0.13			

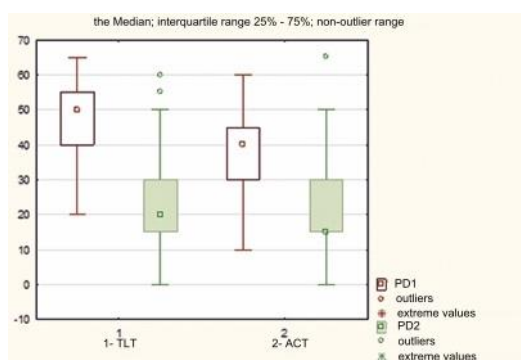


Fig. 2. The dynamics of pulmonary perfusion deficiency after thrombolytic and anticoagulant therapy in the subgroup of intermediate risk of early death.

Notes: PD1 — initial perfusion deficiency; PD2 — changed index of perfusion deficiency as a result of the treatment; ACT — anticoagulant therapy; TLT — thrombolytic therapy

It should be noted that both high-risk and intermediate-risk patients who received thrombolysis were significantly heavier in terms of baseline characteristics: not only a higher percentage of pulmonary perfusion lesions, but also more dignificant dilatation of the right ventricle, higher pulmonary artery pressure and a large proportion of patients with severe and decompensated disorders of the acid-base state.

Of the 169 patients, 15 did not reduce the reduction in perfusion deficiency as a result of the treatment. In the control dynamic study, the indicator remained at the same level or even slightly increased. During thrombolysis, similar observations were more rare: 7 out of 127 (5.5%) versus 8 out of 42 (19%), $p=0.013$, Fisher test, $P = 0.71$.

CONCLUSION

1. Thrombolytic therapy has shown high efficacy in restoring pulmonary perfusion not only in patients at high risk of an early death, but also in the subgroup of intermediate risk.

2. At an intermediate risk of adverse outcome, the strength of the effect obtained from thrombolysis was greater compared with the effect of anticoagulant therapy ($Es=2.16$ and $Es=1.13$).

3. The absence of the effect of recovery of pulmonary perfusion during thrombolysis was noted less frequently as compared with the results of anticoagulant therapy: in 5.5% (95% CI 2.2–11.0) versus 19.0% (95% CI 8.6–34.1).

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