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Research Article

Combined treatment of acute deep vein thrombosis of the lower limbs

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Abstract
The article represents the combined treatment results analysis of 50 patients with deep vein thromboses of inferior vena cava system. The complex clinical and instrumental examination of patients included duplex ultrasound scan, X-ray phlebography, multislice computed tomography with intravenous contrast and radionuclide fleboscintigrahpy. All patients were performed the regional thrombolytic therapy, combined with an open palliative thrombectomy in 19 (38%) patients and endovascular implantation of a temporary or constant cava-filter in 31 (62%) patients. In postoperative period for 12 months' monitoring the local and general complications after combined treatment were found in 4 (8.0%) out of 50 patients, who were performed the combined treatment.

Keywords
deep vein thrombosis; regional thrombolytic therapy; cava-filter; combined treatm ent

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Problem statement and analysis of the recent research

Venous thromboembolic complications (VTEC), including deep vein thrombosis and pulmonary embolism, are the actual problem of modern medicine, being one of the major causes of death and invalidization [1, 2, 3, 4].

In 2004, thanks to the application of epidemiological calculations model, 317 thousand deaths related to pulmonary embolism were diagnosed in the general population of 454 million people in six European Union countries, 34% of cases remained undiagnosed. In 59% of cases pulmonary embolism was diagnosed only after death and only 7% of patients set the correct diagnosis of pulmonary embolism alive [5, 6]. ICOPER register, which included 2,454 patients from 52 centers in 7 countries of the European Union, presented the mortality from pulmonary embolism at the level of 17.4%, which was evaluated in terms of 90 days after discharge from the hospital [5, 7]. The European Society of Cardiology (2014) forecast a doubling of cases of pulmonary embolism in patients older than 40 years during each of the next decade [5].

Pulmonary embolism mortality (PE) reaches 2.1 – 50% in case of deep vein thrombosis (DVT) [8, 9] and in case of resuscitation need the mortality increases to 65% [9]. There often occurs a lightning form of pulmonary embolism – in 31.2 - 43.6% of cases [10].

Every year in Ukraine 50,000 episodes of PE are registered, the level of mortality is 20 – 25% of general hospital mortality [7].

Important fact is that only in 10 – 20% of patients, who died as a result of pulmonary embolism, symptoms of DVT are diagnosed [7, 9], and in 9.2 – 50% of patients with proximal DVT, at the moment of the appeal for medical help, at least one episode of asymptomatic pulmonary embolism was already noted [9]. During next 10 years after the first episode of pulmonary embolism in 30% of patients relapse of pulmonary embolism is observed, the greatest danger of relapse is found in terms of 6 to 12 months after the first episode of pulmonary embolism [10].

Despite of the best efforts, problem of venous thromboembolism remains unresolved. Conservative anticoagulant therapy, which was proposed by majority of foreign and national authors, does not allow the reduction of the incidence of pulmonary embolism and doesn't reduce the manifestations of postthrombosis syndrome. Surgical treatment of deep vein thrombosis effectively prevents VTEC, but because of the late appeal for medical care, opportunities to perform adequate and complete thrombectomy and to prevent the posttrombolitic changes in the late period are limited.

Regional thrombolytic therapy (RTLT) is an alternative way of restoration of patency of thrombolized deep veins. The effectiveness of thrombolytic therapy significantly depends on several factors: time of thrombotic occlusion, it's location, length, thrombolytic drug and way of administration. Objective: to determine the efficacy of the combined methods of the treatment of the deep vein thromboses of the inferior vena cava system and the prophylaxis of the venous thromboembolytic complications.

1. Materials and methods

We have analyzed the examination and combined treatment results of 50 patients with thrombosis of the inferior vena cava (IVC) system in the Department of Vascular Surgery of Transcarpathian Regional Clinical Hospital named after A.Novak for period of 2006 – 2016 years. Men were 18 patients (36.0%) and women were 32 patients (64.0%). The age of patients ranged from 29 to 72 years, average age – was 54±2.3 years.

All the patients had regional thrombolytic therapy (RTLT), which was combined with an open palliative thrombectomy in 19 (38%) patients and endovascular implantation of a temporary or constant cava-filter in 31 (62%) patients (Table 1).

For the examination of patients the laboratory and instrumental methods were used: ultrasound Doppler and ultrasound duplex scanning ("ULTIMA PRO-30, z.one Ultra", ZONARE Medical Systems Inc., USA), radiographic contrast phlebography (DSA, Integris-2000, Philips), multislice computed tomography with intravenous contrast (Somatom CRX "Siemens", Germany, 1994) and radioisotope phleboscintigraphy (emission computed tomography "Tamara").

2. Results and discussion

The duration of the disease has a prior importance for the outcome of treatment. The most effective RTLT is in the earliest period of thrombosis, which, in our opinion, does not exceed 3 – 5 days, when its application allows to save an unaltered intima and venous valves. This feature dramatically reduces contingent of potential patients, for whom the method can be used, because usually quite a long latent period precedes the time of severe clinical manifestations of the disease. Before and after the planned RTLT, besides ultrasound or CT angio regime, the patient was administered a general analysis of blood and urine, biochemical blood analysis, blood group and Rh-factor determinarion, coagulogram (PTI, fibrinogen, INR), a blood test for D-dimer. For the RTLT in case of thrombosis of deep vein of pelvis and lower limbs, we used mainly access through posterior tibialis vena, in which after venotomy conductor was set, and then the catheter. All interventions were performed in operation room with X-ray-control. Through the installed introducer, a conductor and diagnostic catheter was injected endovasculary. The end of the catheter is installed in the affected vessel, and then the conductor should be removed. Radiographic soluble contrast is administered through applied catheter using angiographic injector or syringe, to identify the localization and extent of thrombosis. If the catheter easily passed through the thrombotic masses, the diagnostic catheter was replaced with thrombolytic catheter with multiple openings. If the catheter was easily introduced in X-ray control drirectly into the thrombotic masses, but there was no possibility to bring it through the thrombotic masses, it was replaced with aspiration one, and the tip of catheter was installed near proximal end of thrombotic masses. Then it was slowly removed from thrombotic masses, while introducing thrombolytic solution. During thrombolytic therapy catheter position was daily controlled as the lysis of thrombotic masses, every time setting the catheter at last 3 – 5 cm more distally to proximal border of residual thrombus. RTLT includes several thrombolytic introduction techniques:

1. regional perfusion of the drug, which can be done in two ways: nonselective (end of the catheter is proximally to occlusion and does not reach the areas of thrombosis) or selective (end of the catheter is adjacent to the thrombotic masses);

2. intrathrombotic infusion, during which the end of the catheter penetrates the thrombus, and the operator performs thrombolytic administration;

3. intrathrombotic bolus infusion, in which the end of the catheter is placed distally to thrombosis zone; for this method we use catheter with side holes;

4. gradual infusion, during which the operator at first sets the end of the catheter near proximal end of thrombotic masses and conducts thrombolytic infusion, and then, gradually to the dissolution, end of the catheter is placed distally to complete dissolution of blood clot;

5. prolonged infusion – a standard technique, during which a catheter is installed in the affected area for a long time, during which a thrombolytic agent is administered by pump for microinfusions;

6. graded infusions – thrombolytic agent is injected bolusly in highly concentrated dose, which rapidly dissolves fresh blood clots;

7. forced periodic infusion – catheter is placed inside the thrombus, thrombolytic agent is administered bolusly in large doses every 20 – 30 seconds; the catheter is gradually tighten according to dissolution of thrombotic masses.

Mostly we use a combination of several methods of administration of thrombolytic drug, which we have mentioned above. After finishing the infusion, angiography was performed through selectively installed catheter to assess the outcome of the procedure. In case of satisfactory results, we have finished the procedure. If the result was doubtful, the patient was transferred to the Department of Anesthesiology and Intensive Care, and catheter was placed in the thrombosis area and gradual infusion of thrombolytic drug using a microinfusion pump was performed. During the patient's stay in the Department of Anesthesiology and Intensive Care, constant monitoring of vital functions of the patient and coagulation parameters were conducted (PTI, fibrinogen, INR). If the bleeding was suspected (presence hemorrhage on the tongue, mouth cavity, blood in urine or in stool) or in case of severe coagulopathy, infusion of thrombolytic drug was stopped immediately. After 12 hours control angiography was

Table 1. Combined treatment of patients of main group

		Top of thrombotic/masses									
		Tibial veins		Popliteal veins		Femoral veins		Iliac veins		Total	
RTLT	Combined treatment Implantation of cava-filter Surgical thrombectomy	3 4	7	2 3	5	7 12	19	19 -	19	31 19	50

perfomed through the catheter which was installed before. In case of positive outcome, operation was stopped. If the results were unsatisfactory, operation was continued for another 12 hours in Department of Anesthesiology and Intensive Care, but not more than 24 hours in total.

After finishing the procedure, catheter and introducer were removed. Defect of vessel in place of punction was closed with a device for hemostasis or by using manual compression, at least for 40 minutes. Results were evaluated by ultrasound at the 1-st and the 2-nd days after the procedure.

The effectiveness of the procedure was indicated by: restoration of patency of the vessel not less than for 30%, which is confirmed by instrumental methods of research; absebce of complications; restoration of function of the affected area (reduction of pain and swelling).

In 39 patients (78%) the posterior tibial vein was used. In case of segmental femoral or iliac vein thrombosis and passable distal vein in 11 patients (22%) we used a needle catheter infusion through the femoral or popliteal vein in antegrade direction using the traditional Seldinger method.

As thrombolytic drug we have used streptokinase (n=33) and alteplase (n=17). In case of using streptokinase, its dosage was as following: during first 30 minutes – 250 thousand units intravenously, followed by 100 thousand units every hour for 24 – 72 hours. Total amount of the used drug was 2.65 – 7.45 million units of streptokinase for the course of RTLT.

In case of using alteplase ("Aktelize" produced by the company "Boehringer Ingelheim"), treatment was started with bolus intravenous administration of 5 mg for 2 minutes and then continued infusion with a speed of 1 mg/hour for 1 - 3 days before the appearance of angiographic signs of restoration of patency of the affected vein segments. The total number of alteplase administered to treatment was 25 - 75 mg.

After finishing RTLT patient was administered low molecular weight heparin at therapeutic doses based on patient body weight, or rivaroxaban/dabigatran in therapeutic doses. Rivaroxaban was administered at the dose of 20 mg – once per day, and dabigatran 150 mg – twice per day for 3 - 6 - 12 months.

During the conducted RTLT, fibrinogen level should be between 1.5 - 2 g/l. By reducing the level of fibrinogen to 2 g/l or lower, infusion rate of trombolitic drug was reduced twice (until increased fibrinogen level). By reducing the levels of fibrinogen to 1.5 g/l, RTLT was stopped and heparin infusion was started under the control of activated partial thromboplastin time. Indexes of coagulation were evaluated every 6 hours.

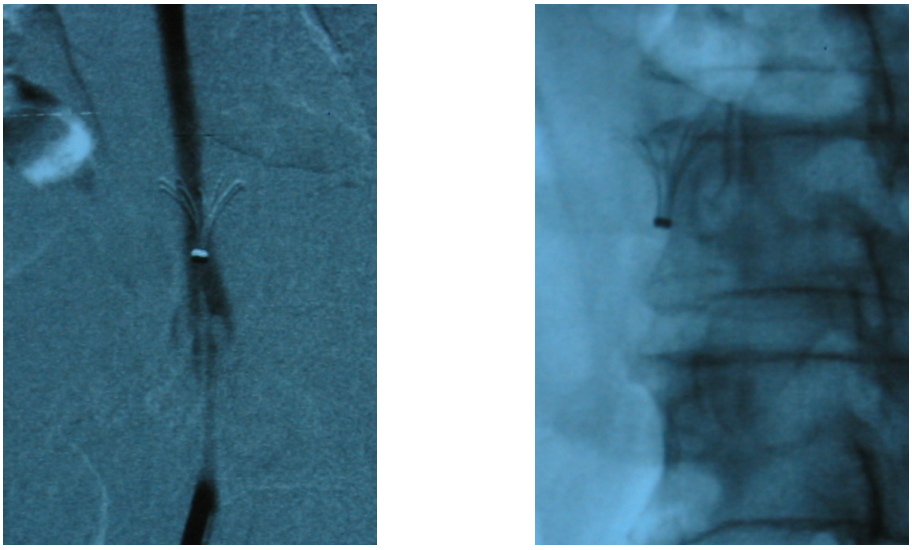
During RTLT there was a real danger of PE in system of vena cava inferior (VCI) that is why for the prevention of complications in 31 patients (62%) endovascular implantation of a temporary or permanent cava-filter (CF) was used. Implantation of CF in lumen of VCI allows to delay all particles ranging in size from 2 to 4 mm, depending on the design of the filter, that significantly reduces the risk of VTEC, but does not affect the flow in the VCI. Temporary CF was established in 28 patients (90.3%), permanent in 3 (9.7%). Indications for implantation of permanent CF were recurrent pulmonary embolism on the background of repeated DVT. In case of implantation of a permanent CF in 2 patients CF "Osot" (Ukraine) and in 1 patient CF "Cordis TrapEase" was used.

Duration of intervention usually does not exceed 40 – 60 minutes. CF was implantated distallly to renal veins under control of X-ray after finishing of diagnostic angiographic study, through percutaneous access through the femoral (n=27) or subclavicular (n=4) veins under local anesthesia. Transportation of CF was performed using the catheter with size from 5 to 11 Fr through introducer with size from 6 to 12 Fr. The length of the catheter-conductor was 65 cm (for subclavicular access) or 85 cm (for femoral). Using a special device, CF was moved into the lumen of the vessel and fixed to its walls. Under X-ray control CF was placed at level of L1 - L2 vertebra. Before endovascular implantation of CF, we've necessarily calculated the size of VCI using ultrasound, for the purpose of personal selection of CF according to VCI diameter and to prevent its migration. After setting CF during X-ray control, necessarily evaluated the place of implantation of the filter, its location in relation to the longitudinal and transversal axis of the vessel, absence of perforation of vessels (contrast output beyond vessels).

After implantation of CF within 1 - 2 days limitation of physical activity and bed rest were prescribed. After finishing of the RTLT, indirect anticoagulants and venotonics were administered (normoven 1 tab. 2 times a day after meals for 2 months), application of elastic bandage, clinical supervision of vascular surgeon at least 1 time per month with ultrasound control of CF status.

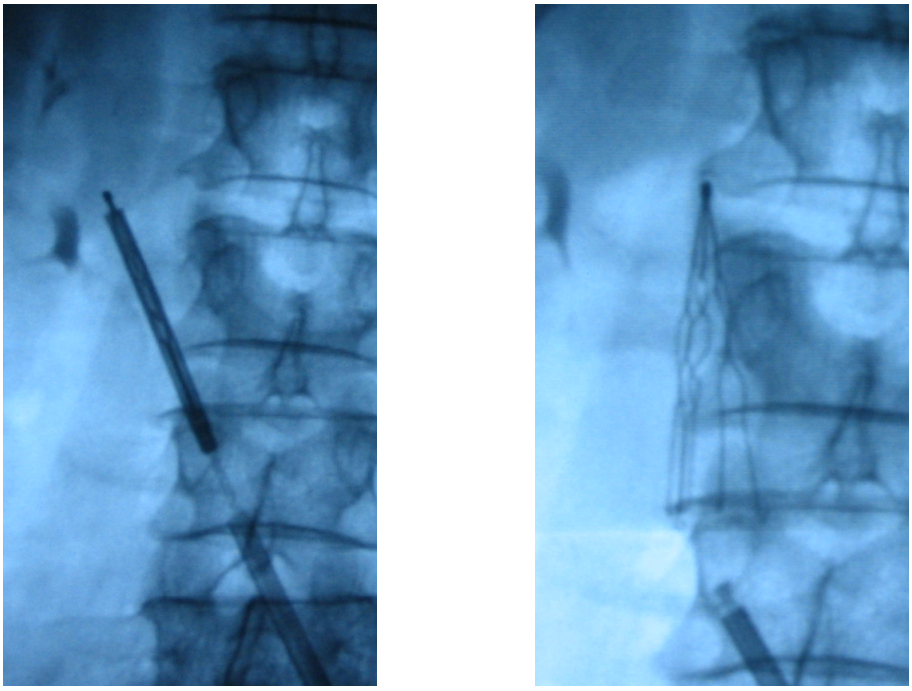
In order to set endovascular implantation we used CF of the following brands: REPTELA (n=10), Osot (n=8) (Figure 1), Greenfield (n=4) (Figure 2) and Cordis (n=9) (Figure 3).

Cava-filters "Osot", which are producted by Endomed (Ukraine), are produced since 1996 year. CF "Osot" consists of eighteen arched curved legs, which in one end are collected



(a) **(b)**

Figure 1. Endovascular implantation of cava-filter “Osot” in the inferior vena cava: deployment of filter construction (a), final form (b).



(a) **(b)**

Figure 2. Endovascular implantation of cava-filter ≪Greenfield≫ in the inferior vena cava: conductor in the lumen of vein (a), deployment of cava-filter construction (b).

in holder and are placed in two layers (for 9 feet). In a working condition CF is fixed by legs in the wall of blood vessels, which are putting pressure on the wall of vessel due to elastic deformation forces. CF “Osot” is produced in two versions – temporary (with loop on the end of filter holder for extraction) and permanent filters (without loop). Legs of CF are placed in the direction of blood flow, so the filter element “crowding out” the embolus to the periphery of the vessel and leaving a significant portion of the lumen of VCI free, which reduces barriers to blood flow and reduces the risk of formation of cava-syndrome. Temporary CF “Osot” was implanted in 6 patients. In 2 patients, as it was mentioned above, we performed

implantation of permanent CF.

In 1 patient we implanted permanent KF "Cordis TrapEase". In 8 patients we implanted a modified construction of CF "Cordis" for temporary implantation "OptEase", which is distinguished by hook on the caudal end for removing. Period for removing CF "Cordis OptEase" is limited to 12 days.

Duration of temporary implantation of CF is ranged widely from 12 to 80 days, in average it was 39.5 days. Thus, using of temporary CF "Osot" and "Cordis OptEase" duration of its implantation does not exceed 12 - 14 days, "Greenfield" – 45 - 50 days, REPTELA – 70 - 80 days. Indications for removing of temporary CF were not only the manufacturer's recommendations, but presense of persuasive evidence of absence of a danger of pulmonary embolism. After receiving information about liquidation of danger of PE, temporary CF was removed by endovascular intervention under X-ray control.

To reduce the amount of thrombotic masses, artificial recanalization, creating better conditions for thrombolysis and release of the major collectors in 19 patients we used a combination of surgical thrombectomy and RTLT. After thrombectomy, even in case of uncompletely freed vein lumen from the thrombotic masses, in conditions of artificial recanalization, contact of drug with thrombus was in a much larger area. Surgery intervention improves venous outflow from the affected limb and local hemodynamics. Role of RTLT after surgical thrombectomy is to attempt to perform complete dezobstruction of main veins of limbs and prevention of rethrombosis in the nearest postoperative period (Table 2).

Combination of thrombectomy with RTLT, unlike isolated thrombectomy, allowed restoring deep vein lumen and preventing the postthromboflebityc syndrome in patients with DVT. Mostly RTLT was performed after open thrombectomy of the femoral vein – in 12 patients. Less often RTLT was performed after thrombectomy of tibial and popliteal veins – in 4 and 3 patients, respectively. Open thrombectomy and RTLT were performed with the help of method, described above.

After the combined treatment in postoperative period for 12 months of observation the local and general complications were found in 4 (8.0%) out of 50 patients, who completed the combined treatment.

In 2 patients after open thrombectomy from common femoral vein followed by RTLT, we have observed the limforrhea from postoperative wound in the groin, which has solely stopped after 11and 15 days respectively. In 1 patient marginal necrosis was observed in the area of wound in the groin. There were no purulent-septic complications in the postoperative wounds. In 1 patient during the first 4 days after the beginning of RTLT, short-term local bleeding and small subcutaneous bruising in the area of injection were observed, which were eliminated with more prolonged compression of the injection sites. Bleedings of other genesis and other complications in the immediate postoperative period were not observed.

Length of patients' stay in hospital after combined treatment of thrombosis of IVC systems ranged from 12 to 16 days, an average of 13 ± 1.3 days. There were no lethal cases.

Conclusions

1. Combined treatment is effective and justified in the treatment of common forms of venous thrombosis of the inferior vena cava system, but it needs further improvement and development.

2. The most safe in means of bleeding complications are the options when surgical intervention is preceded by thrombolysis or is executed during the actual intervention.

3. The best prospect is the combination of several methods of blood flow restoration for different segments (primarily open thrombectomy) and the temporary prevention of pulmonary thromboembolism (application of temporary cava-filters models).

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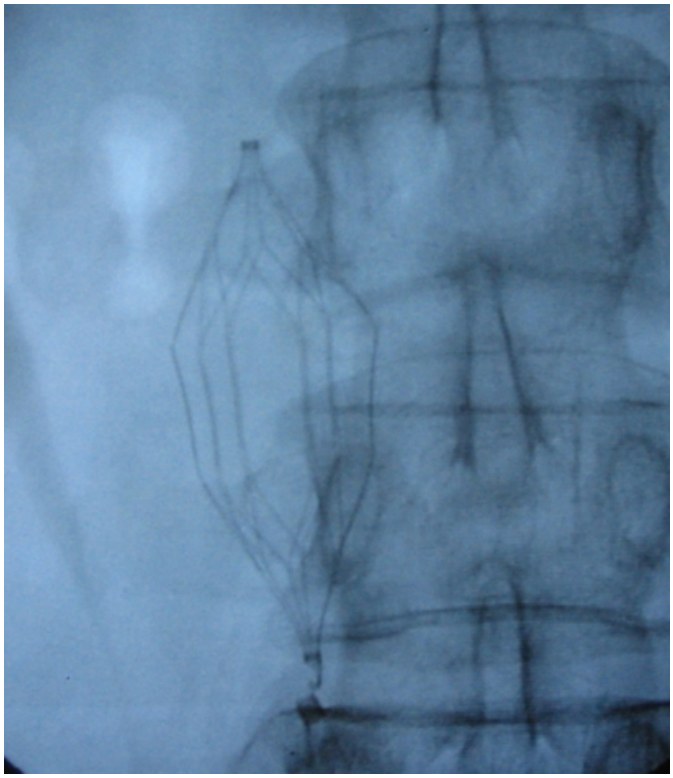

Figure 3. Endovascular implantation of cava- filter “Cordis OptEase” in the inferior vena cava.

Table 2. The combination of surgical thrombectomy and regional thrombolytic therapy

Combined therapy		Abs. (%)
Regional thrombolytic therapy	Thrombectomy from tibial vein	4 (21.0%)
	Thrombectomy from popliteal vein	3 (15.8%)
	Thrombectomy from superfisial femoral vein	3 (15.8%)
	Thrombectomy from common femoral vein	9 (47.4%)
Total		19 (100%)

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