Thrombolysis of Acute Arterial Occlusion with rt-PA

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ABSTRACT

The use of thrombolytic agents to treat peripheral arterial occlusions is a new method. Despite its advantages, information about complications caused by the use of rt-PA and about its place in treatment is still incomplete. The aim of this study was to establish a dose range for rt-PA and to follow the patients with a protocol during and after thrombolysis.

Between May 1999 to January 2000, 14 patients with symptoms of peripheral arterial occlusion came to Istanbul Medical Faculty Emergency Surgery Unit. The duration of ischaemia before their hospitalization took an average of 44 hours. (Range 3 hours-7 days). A pulse-spray catheter was directed to the thrombus under angiographic control. Bolus injection of 5 mg of rt-PA was followed by 15 minutes of interval. The extent of thrombolysis was checked by angiography and then bolus injection of 5 mg of rt-PA was repeated. After angiographic control, patients having insufficient thrombolysis, received 0.05 mg/kg/hour of infusion for 12 hours. At the end of 12 hours, thrombolytic treatment ended with a control angiography. A thromboembolectomy operation was made to patients still having an occlusion after thrombolysis. To avoid re-occlusions, all of the patients received 1.5 mg/kg/day low molecular weight heparin (enoxaparin) for 1 week. At the end of thrombolysis, 9 patients had complete lysis. A patient, having an occlusion in superior mesenteric artery had 60% recanalisation. 2 patients (14%) having 90% stenosis, needed a balloon angioplasty besides thrombolysis, and both of them had complete reperfusion. 2 patients (14%) needed a thromboembolectomy operation due to insufficient thrombolysis. 2 patients (14%) had a minor bleeding after thrombolytic treatment. After thrombolysis, 2 patients (14%) had a stroke. There were no amputations. 1 of the patients having a stroke, died 2 days after thrombolytic treatment 1 patient died due to myocardial infarction during thrombolysis. 1 patient (7%) died due to diabetic coma on the 20th day. Acute myocardial infarction was the cause of death in 1 patient on the 25th day.

In conclusion pulse spray thrombolysis with rt-PA is safe and efficient. Moreover there is a reduction in complications and need for surgical procedure. The recent problem is to find the optimum dosages for the best thrombolysis and for least complications.

Key Words: Thrombolysis, Acute arterial occlusion, rt-PA, Pulse spray catheter.

Turk J Haematol 2001;18(3):165-172.

INTRODUCTION

Acute peripheral arterial obstruction is a significant cause of limb loss. Amputation was the only treatment, in gangrenes caused by acute arterial occlusions until the 1940's[1]. This was followed by embolectomy and by operative revascularization trials. Today, intra-arterial thrombolytic therapy is used as an alternative to surgical treatment methods, to restore arterial circulation in acute peripheral arterial occlusion. Streptokinase (SK), Urokinase (UK) and recombinant tissue plasminogen activator (rt-PA) are the agents used in thrombolytic therapy.

Due to recombinant DNA technology, the tissue plasminogen activator (rt-PA) (Alteplase, Actilyse, Boehringer), which is the most preferred among these agents, is available for clinical use. This agent is fibrin specific and its reperfusion time is shorter than urokinase or streptokinase[2,3]. In addition to that, different than streptokinase, rt-PA doesn't have an antigenic nature so it doesn't cause allergic reactions when used more than once.

Despite its advantages, information about complications caused by the use of rt-PA and about its place in treatment is still not complete. And there are not enough studies that are made to form a safe protocol for the use of rt-PA in the treatment of acute peripheral arterial occlusions. It is reported that increasing the dosage of rt-PA increases the efficacy of thrombolysis but may also increase the risks[4].

The aim of this study was to establish a dose range for rt-PA and to follow the patients with a protocol during and after thrombolysis.

MATERIALS and METHODS

Between May 1999 and January 2000, patients who came to Emergency Surgery Department of Istanbul Medical Faculty with peripheral arterial occlusions were chosen for this study. Patients had clinical symptoms and signs as pain, pallor, poikilothermia, paraesthesia and paraplegia. Pulseless arteries were examined by Doppler and ankle-brachial index was measured.

Inclusion Criteria: Those having symptoms of peripheral arterial occlusion, were included in the study after being examined and verified with angiography.

Exclusion Criteria: Patients with re-occlusion after a prior thrombolysis, those having a stroke, those who needed urgent exploration because of severe ischaemia, or those having a high bleeding risk were not included in the study.

Treatment Protocol: A pulse-spray catheter was directed to the thrombus under angiographic control. Bolus injection of 5 mg of rt-PA was followed by a 15 minutes interval. The extent of thrombolysis was checked by angiography and then bolus injection of 5 mg of rt-PA was repeated. After angiographic control, patients having insufficient thrombolysis, received 0.05 mg/kg/hour of infusion for 12 hours. At the end of 12 hours, thrombolytic treatment ended with a control angiography. A thromboembolectomy operation was performed on patients still having an occlusion after thrombolysis. Moreover, to avoid re-occlusions, all of the patients received 1.5 mg/kg/day low molecular weight heparin (enoxaparin) for 1 week. The algorithm of our treatment protocol is shown in Figure 1.

Treatment was considered successful if pain dissapeared and/or pulses were restored, and if revascularisation was verified with angiography.

One week after thrombolysis, patients were re-examined; during their physical examination, their cardiac functions were checked with echocardiography. Those having a source of embolus, were given oral anticoagulant (coumadin) for life time use.

RESULTS

14 patients were taken in to the study. There were 8 males' (57%) and 6 females (43%) with an average age of 66 (range 55-90). Patients had clinical signs of peripheral ischaemia as pain (14 patients-100%), pallor (14 patients-100%), poikilothermia (14 patients-100%), cyanosis (2 patients-14%) and paraesthesia (2 patients-14%). The duration of ischaemia before their hospitalisation took an average of 44 hours. (3 hours-7 days). The shortest occlusion was 6 cm and the longest was

45 cm. The average length of occlusions was 16 cm. Occluded arteries were superior mesenteric artery (1 patient-7%), femoropopliteal artery (2 patients-14%), iliofemoral artery (3 patients-21%), popliteal artery (4 patients-29%), posterior tibial artery (1 patient-7%), brachial artery (2 patients-14%), and common iliac artery (1 patient-7%). Occluded arteries are shown in Figure 2. Symptoms and signs observed are given in Table 1. All patients were examined for their prior dise-

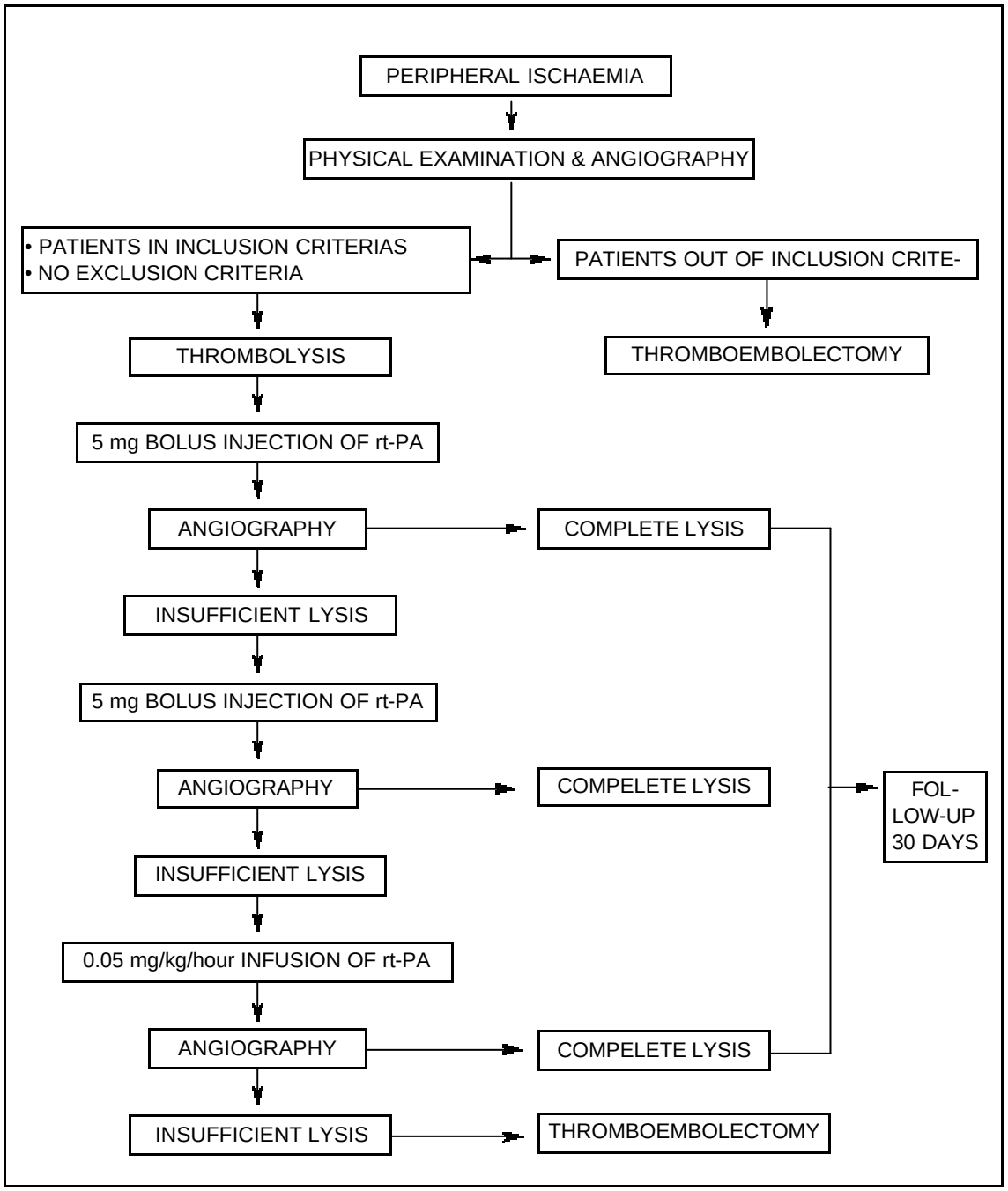

Figure 1. Algorithm of our study.

ases that are given in Figure 3.

12 patients had an emboli and 2 had acute thrombosis. Besides thrombolysis a balloon angioplasty was performed on patients having acute thrombosis.

43% of the patients had a cardiac disease, 36% had diabetes and 36% had hypertension.

Recanalization: At the end of thrombolysis, 9 patients had complete lysis. One patient, having an occlusion in superior mesenteric artery had 60% recanalisation. 2 patients (14%) having 90% stenosis, in the part of the superior femoral artery found in Hunter's channel, needed a balloon angioplasty following thrombolysis, and both of them had complete reperfusion. 2 patients (14%) needed a thromboembolectomy operation due to insufficient thrombolysis.

Complications: 2 patients (14%) had a minor bleeding after thrombolytic treatment. Minor bleedings were localised in gums and nose. These patients had no other complications and they had 100% reperfusion. After thrombolysis, 2 patients (14%) had a stroke. There were no amputations.

Mortality: One of the patients having a stroke, died 2 days after thrombolytic treatment.

1 patient died due to myocardial infarction during thrombolysis.

Follow-Up (30 days): 1 patient (7%) died due to diabetic coma on the 20th day. Acute myocardial infarction was the cause of death in 1 patient on the 25th day.

DISCUSSION

Alteplase is a tissue plasminogene activator produced by recombinant DNA technology. This enzyme is produced by the implantation and incubation of the tissue plasminogene activator gene (complementary DNA), taken from human melanoma cell, into the ovary of a Chinese hamster.

"Pulse-Spray" infusion catheters are used in thrombolysis. With this catheter, thrombolytic agents can be injected in to the thrombus with a high pressure, that's how the thrombus is separated into smaller parts and the surface of reaction is increased. Pulse-Spray technique is used to increase the speed of thrombolysis and to decrease the duration of therapy. However, it has been reported that after an anterograde flow in the vessel has been obtained, pulse-spray infusion catheters are not superior to classical infusion catheters[8-10].

Thrombolytic therapy is also made with streptokinase and urokinase. Thrombolytic agents were compared in different studies. For the study of Braithwaite et al, rt-PA is faster and more effective than streptokinase[3] but for STILE trial, made with 393 patients, t-PA is not different than urokinase or streptokinase[11]. For streptokinase, infu-

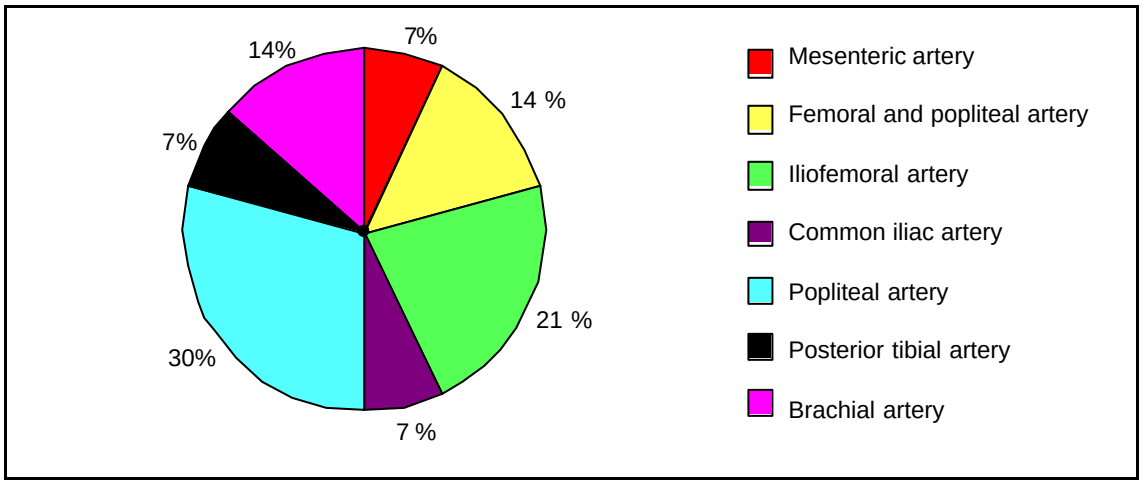

Figure 2. Occluded arteries.

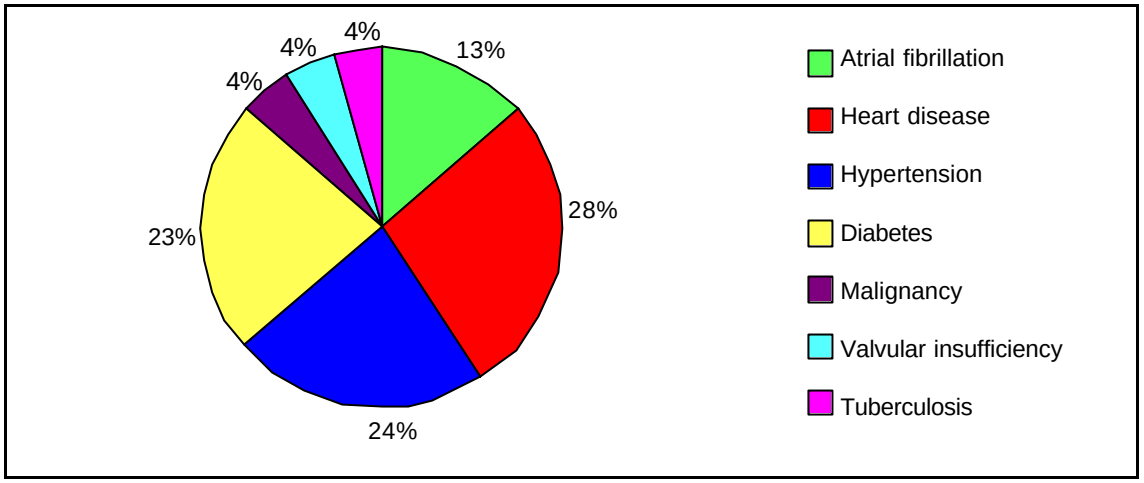

Figure 3. Concomitant diseases

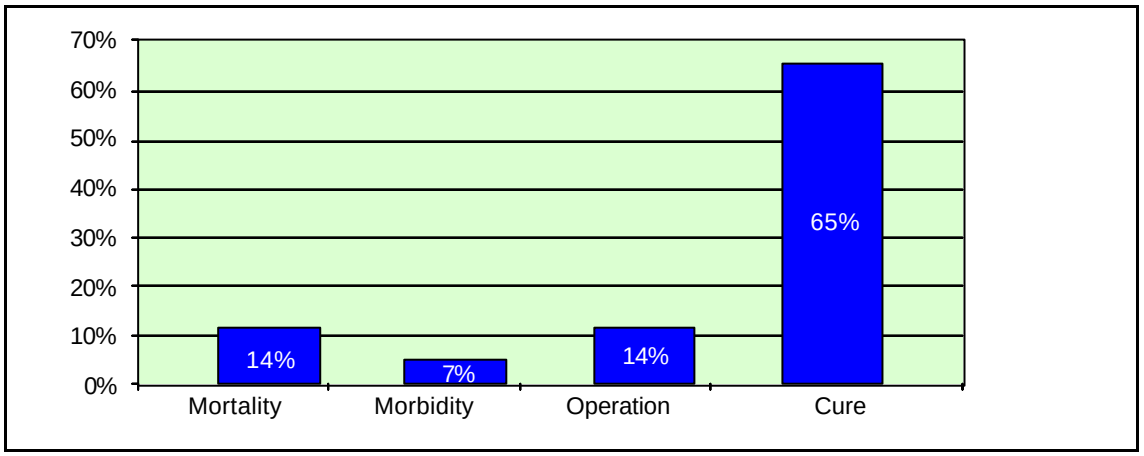

Figure 4. Concomitant diseases

sion times longer than 96 hours have been reported[5]. Today, urokinase is not available any more. Anaphylaxis is rare with any of the thrombolytic agents, but allergies characterised by early flushing, vasodilatation, rashes and hypotension are a complication with streptokinase. In different studies, though rt-PA is faster than SK and UK, and though it doesn't cause allergic reactions, important differences have not been reported[6].

Thrombolytic therapy is a medical treatment. That's why, it doesn't cause surgical complications as in thromboembolectomy. In a study made in the General Surgery Department of Istanbul Faculty of Medicine, it has been observed that thrombolytic therapy needs a shorter hospitalisation period than surgical treatment. Thromboembolectomy and thrombolysis, had a similar rate of mortality (14% and 11.7% respectively)[7] but limb salvage rate was much higher with thrombolysis (the amputation rate was 15.9% for thromboembolectomy and 0% for thrombolysis). Moreover, although rt-PA is expensive, in total price, thromboembolectomy costs more than thrombolysis. According to STILE trial and Mc Namara, surgical reconstruction is better than thrombolysis in chronic ischaemia caused by thrombosis, but the results of therapy are better in thrombolysis in acute ischaemia (< 14 days). However, there was no

Table 1. Patients

	Age	Sex	Duration of ischaemia	Pain	Pallor	Poikilo-thermia	Cya-nosis	Parest-hesia	Length of occlusion	Occluded artery	Concomitant Diseases	Early Results
Patient 1	72	F	3 days	x	x	x			5cm	Sup. Mes.		Cure
Patient 2	60	M	7 days	x	x	x			7cm	Fem & Pop		Cure
Patient 3	70	F	5 days	x	x	x			40cm	Fem & Pop	AF	Cure
Patient 4	50	M	7 hours	x	x	x			20cm	Iliofemoral	Lymphoma	Cure
Patient 5	73	F	4 hours	x	x	x			15cm	Popliteal	HD, HT, Diabetes	Cure
Patient 6	54	M	1 day	x	x	x			7cm	Post. Tibial	Diabetes	Cure
Patient 7	55	M	3 day	x	x	x			10 cm	Brachial	Valvular Insuff.	EX
Patient 8	90	F	6 hours	x	x	x	x		12 cm	Popliteal	Tuberculosis	Embolectomy
Patient 9	50	M	1 day	x	x	x			25cm	Iliofemoral	HD, AF, HT	Embolectomy
Patient 10	61	M	3 hours	x	x	x			6 cm	Com. iliac	Diabetes, HT	Cure
Patient 11	68	M	2 days	x	x	x	x	x	45 cm	Iliofemoral	HD, HT, Diabetes	Cure
Patient 12	64	F	8 hours	x	x	x		x	10cm	Brachial	HD, AF, Diabetes	EX
Patient 13	86	F	12 hours	x	x	x			15 cm	Brachial	HD	Cure
Patient 14	70	M	2 days	x	x	x			12 cm	Popliteal	HD, HT	Stroke

AF: Atrial fibrillation HD: Heart Disease HT: Hypertension

difference in amputation and in mortality rates[11-12]. In acutely occluded arteries, the cause of this difference was reported to be the low pressured reperfusion or the lysis of the thrombosis in the out-flow arteries[13,14,16]. In our study, all occlusions progressed acutely and the etiology was thought to be thrombosis. In 2 patients having thrombosis, angioplasty was added to thrombolysis to obtain revascularization.

In thrombolysis with rt-PA, a safe protocol couldn't be established. The doses are between 0.05 and 0.1 mg/kg/hour or between 0.25 and 10 mg/kg. In most of the studies made with rt-PA, it has been reported that the increasing dosages are not increasing the effect and the most effective dosages were reported to be 1 mg/hour or 0.05 mg/kg/hour[9,10,17,18]. There is no clear information about bolus injection. 0.05 mg/kg/hour infusion added to 5 mg bolus injection that we used in our study, was not used before. Observing the 19 prospective studies made by Berridge between 1974-1988, the incidence of haemorrhagic stroke is 1% and the incidence of major haemorrhage is 5.1% [19]. The incidence of stroke (haemorrhagic or ischaemic) observed in thrombolysis with low doses is reported 2.3% (27/1157)[20], 1.2% and 2.1%[21] in literature. Although these incidences are lower than 14% that we had in our study, there are big differences in the number of patients and in population types in different studies. The bolus injection that we use, can be a factor increasing the mortality and the morbidity of our study. In a study made by Decrinis et al with 210 patients. 10 mg rt-PA was combined with 3000 IU heparin and the mortality rate was reported 0%. However, in 30 days follow up, 2 patients (1%) died due to CVA[5]. The best results in literature were obtained with the long time infusion of low-dose rt-PA and it has been decided that it would be better to follow patients in intensive care unit[22].

In the studies made, it has been observed that there is not a correlation between the length of occlusion in embolic occlusions and the rate of reperfusion. The cause of this, is thought to be the improbability of forming collaterals in embolic occlusions which causes the length of the occluded section to be estimated longer that it actually is. However, in thrombotic occlusions, as collaterals

are formed, there is a correlation between the appearance of a nonoccluded artery in angiography, and the rate of reperfusion. In an other study, with the increasing length of an occlusion, the rate of complete recanalization decreases from 63% to 42% and also, the percentage of partial recanalization increases from 12% to 29%[5]. Moreover, as the length of the occluded segment increases, the frequency of complications increases too. In our study, in 2 patients only partial recanalization could be obtained by thrombolysis, but in the same session complete recanalization could be obtained by adding more TPA.

Thrombolytic therapy is also used in aneurysm surgery. Due to thrombolytic therapy applied during the operation, the arteries distal to the aneurysm, can easily be cleaned with thrombolysis. In our clinic, in 2 patients we applied thrombolytic therapy during a popliteal aneurysm operation, with good results. In literature, there are also studies which combine thrombolysis with endovascular surgery.

Pulse-spray thrombolysis is an alternative treatment to surgical treatment with at least equal results. In order to make it safer and more effective, more trials are needed. As in our study, the mortality rate was high in patients who had bolus injection and infusion together, we believe we may have better results with long time infusion with lower dose. We believe, as the number of trials increases, the optimal dose and protocol will be established, and thrombolysis will be the ideal and the most preferred treatment method in the future.

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