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Review Article

Thrombolytic Therapy in Acute Ischemic Stroke

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Abstract
The discovery of thrombolytic agents goes back to the 1930s. The general action of thrombolytic agents is to convert plasminogen to plasmin, which degrade fibrin clots. Thrombolytic therapy has been emphasized in clinical practice for its rapid action, high efficacy and better outcome in a precise time window. For Acute Ischemic Stroke the time window for the National Institute of Neurological Disorders and Stroke (NINDS) is less than 3 hours of symptom onset and for the European Cooperative Acute Stroke Study (ECASS III) is between three to four and half hours from symptom onset. This review paper aims to give a systematic overview and to acknowledge the use of thrombolytic therapy in Acute Ischemic Stroke.
Keywords: Acute Ischemic Stroke, thrombolytic therapy, thrombolytic agents.

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Introduction

In nineteen thirties researchers came across thrombolytic agents, discovered that filtrates of broth cultures of certain strains of hemolytic Streptococcus bacteria could dissolve fibrin clot. But it was only in 1958 that thrombolytic therapy was first used to treat Acute Myocardial Infarction (AMI) patients. In that same year 3 patients were treated with thrombolytic therapy for Acute Ischemic Stroke (AIS). After that thrombolytic therapy started its journey in clinical trial, opening the way for the appearing of three generations of thrombolytic agents. Every year the incidence of AIS is about 700, 000 people with 61, 000 deaths, an urgent and early treatment for AIS promises better neurological outcomes. The US Food and Drug Administration (FDA) approved alteplase, a second generation of thrombolytic agent, to be the only drug used in the treatment of AIS. Other intravenously administered thrombolytic agents, including reteplase, urokinase, and staphylokinase have been considered for treatment of patients with AIS. However, none of these agents have been extensively tested. In the next session we discuss the history, mechanism of action, agents of thrombolysis, inclusion and exclusion criteria for thrombolytic therapy and the side effects of the therapy.

History

The discovery of thrombolytic agents goes back to the 1930s, when it was shown that substances derived from bacteria (streptokinase, Staphylokinase), tissue (Fibrinokinase), urine (Urokinase) or bat saliva could activate the fibrinolytic system [1]. In 1933, Tillet and Garner reported that, Lancefield Group, a beta-hemolytic streptococci was capable of producing a fibrinolytic substance which later was named streptokinase [2, 3]. They also showed that filtrates of broth cultures of certain strains of hemolytic Streptococcus bacteria could dissolve fibrin clot [4]. Later In 1952, Johnson and Tillet pursued and achieved thrombolysis of experimental thrombi in rabbit ear veins by administration of streptokinase through a peripheral vein [3]. The first clinical use of streptokinase happened in 1958, its relative success in treating Acute Myocardial Infarction (AMI) patients, changed the focus of treatment, in that same period Sussman and Fitch reported the first attempt to treat Ischemic Stroke using thrombolysis [5, 6, 7]. They treated three patients with plasmin (fibrinolysin). One patient had moderate clinical improvement with recanalization of the Middle Cerebral Artery (MCA), the other two did not show clinical improvement, since computer tomography (CT) was not available until the mid-70s it was not possible to overrule Intracerebral Hemorrhage (ICH) [1]. These early studies triggered interest in developing fibrin-specific agents for thrombolytic therapy [8]. Around 1980, through recombinant technology, multiple second and third generation lytics were developed and tested clinically, tissue plasminogen activator (t-PA) was purified by Collen D, Lijnen HR and Rijken DC, Collen D [9, 10, 11]. In December 1995, results from the National Institute for Neurological Disorders (NINDS) Recombinant Tissue Plasminogen Activator (rt-PA) Stroke Trial were published. Favorable outcomes were achieved in 31% to 50% of patients treated with rtPA and 20% to 38% of patients given placebo. The major risk of this type of treatment was symptomatic intracranial hemorrhage, which occurred in 6.4% of patients treated with rtPA and in 0.6% of patients given

placebo. Intravenuous-thrombolysis for Ischemic Stroke began its wide spreading. In June 1996 the FDA approved intravenous tissue plasminogen activator (t-PA) for the treatment for AIS, based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) study [12]. After that other clinical trials were publish on the thrombolytic therapy in the first, second and third European Cooperative Acute Stroke Study (ECASS I, II, III) and Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) and more other trials.

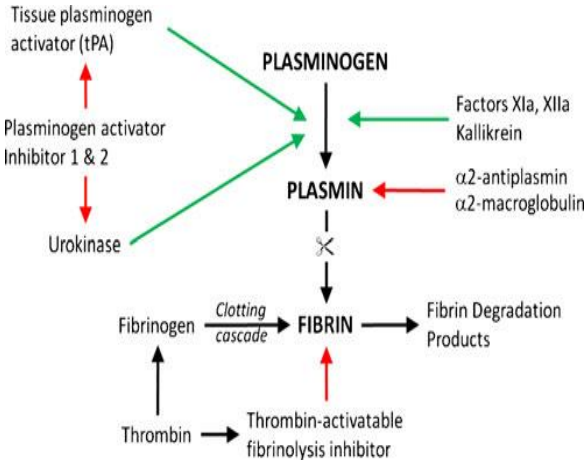
Mechanism

The term thrombolytic is usually synonymous with fibrinolytic. In the context of Ischemic Stroke, thrombolytic specifically relates to degradation of fibrin, the tough net-like backbone of a clot that is blocking flow to a portion of the brain. The clot can form in-situ (i.e., a thrombus) or can travel from another source, such as a tight carotid stenosis or the heart (i.e., an embolus) [9]. In a general action we will say thrombolytic agents convert plasminogen to plasmin, which degrade fibrin clots. From a clinical standpoint, a thrombolytic is a drug that is delivered for the purpose of recanalization of the occluded artery and reperfusion of ischemic, but still salvageable brain tissue(i.e., ischemic penumbra)[9]. The concept of ischemic penumbra was first introduced by Astrup and colleagues in 1981 as "hypo perfused brain tissue which has capacity to recover if perfusion is improved" [13].This area of brain tissue regains its function if the occluded blood vessel is recanalized and is the key target for thrombolysis [13].

The efficacy of thrombolytic drugs depends on a few important factors: 1) the age of the clot can reduce the efficacy of the thrombolytic, older clots tend to have more fibrin crosslinking and are more resistant to thrombolytic; 2) the specificity of the lytic for fibrin will determine its activity; 3) half-life and the presence of any neutralizing antibodies are other determinants of efficacy [9].

Thrombolytics can be divided into two different categories: fibrin-specific thrombolytics and non-fibrin-specific thrombolytics. In the fibrin-specific drug group there is Alteplase, Reteplase, and Tenecteplase, the non-fibrin-specific drugs include Streptokinase or Staphylokinase. Alternatively, lytic that convert plasminogen into plasmin can be described as direct versus indirect. Direct activators are the same as those previously listed for fibrin-specific drugs. Indirect activators of plasminogen include Streptokinase, Staphylokinase, and Desmoteplase (vampire bat plasminogen activator). Direct activators are all serine proteases that cleave a single (arginine-valine) amino acid bond to yield plasmin. Indirect activators are not proteolytic, but rather form a complex with plasminogen which can then convert additional plasminogen to plasmin [9]. After the formation of a mass of aggregated platelet that accelerates the clotting factors, most of the time thrombin that reacts with fibrinogen to form fibrin monomers that are then polymerized to from fibrin clots. Thrombolysis activates plasminogen, which in turn forms plasmin proteolytic enzyme capable of breaking cross-links between fibrin molecules. Thrombin activates Factor XIIIa a blood proenzyme to increase the resistance of the clot to fibrinolysis by cross-linking individual fibrin monomers, other substances present in the blood inhibit the fibrinolytic pathway. This mechanism is illustrated by the Figure 1.

Figure 1: Mechanism of thrombolytic therapy



Note: Important endogenous substances and factors involved with clot formation. Green arrows indicate induction and red arrows inhibition [9].

Thrombolytic agents

Multiples methods such as intravenous, intra-arterial or by a long catheter that delivers drugs directly to the site of the blockage are used to apply thrombolytic therapy. The intravenous route is the most commonly used route for administering thrombolytic therapy for AIS [14]. The thrombolytic agents available today are serine proteases that work by converting plasminogen to the natural fibrinolytic agent plasmin. Plasmin lyses clots by breaking down the fibrinogen and fibrin contained in the clot [14]. Fibrinolytic agents, are classified into first generation (streptokinase, Urokinase), second generation (recombinant tissue plasminogen activator (t-PA or rt-PA), Pro-Urokinase) and third generation (Reteplase (rPA), Tenecteplase (TNK-tPA)).

Streptokinase

Streptokinase is produced by beta-hemolytic streptococci. By itself, it is not a plasminogen activator, but it binds with free circulating plasminogen (or with plasmin) to form a complex

that can convert additional plasminogen to plasmin. The FDA approved regimen for pulmonary embolism is 250, 000 U as a loading dose over 30 minutes, followed by 100, 000 U/h over 12-24 hours [15]. Streptokinase is the least expensive fibrinolytic agent, but unfortunately, its antigenicity and its high incidence of untoward reactions limit its usefulness in the clinical setting. Streptokinase is produced from streptococcal bacteria, it often causes febrile and other allergic reactions. Several trials, such as Multicenter Acute Stroke Trial-Italy(MAST-I), Multicenter Acute Stroke Trial-Europe(MAST-E) using streptokinase for the treatment of AIS were terminated due to excessive early mortality in the treatment groups. These trials administered 1.5 million units over a period of one hour to patients within 4 to 6 hours of symptom onset. In the MAST-E the mortality rate at 10 days was significantly higher in the streptokinase group than in the control group mainly due to hemorrhage.

Urokinase (Abbokinase)

Urokinase (UK) is sometimes referred to as urinary-type plasminogen activator (uPA) because it is secreted by the kidneys and is found in urine. It has limited clinical use because it produces considerable fibrinogenolysis. Urokinase regimen for PE consists of 4400 U/kg as a loading dose given at a rate of 90 mL/h over a period of 10 minutes, followed by continuous infusion of 4400 U/kg/h at a rate of 15 mL/h for 12 hours [14]. In plasma, Urokinase has a half-life of approximately 20 minutes. Allergic reactions are rare, and the agent can be administered repeatedly without antigenic problems. In early studies of thrombolytic therapy for AIS using either SK or UK, intracerebral hemorrhage was a leading cause of death, and no clear benefit was seen.

Urokinase has limited clinical use due to its fibrinogensis. Andrew Bivard et al., Murray et al. tested for both intravenous and intra-arterial thrombolysis, but it has not shown significant clinical outcomes improvement. Tirschwell DL et al. reported in a series of 43 patients treated with intra-arterial urokinase for AIS that dose higher than 1,500,000 U was implicated as a predictor of serious complications in 37% of patients. Sugg RM et al. compared intra-arterial Reteplase to Urokinase for thrombolytic recanalization in AIS. 22 patients received UK mean doses were 690,000 +/- 562,000U, recanalization rates were 64% and symptomatic intracerebral hemorrhage rates were 4.5%, the mortality rate was 27% with UK. More retrospective or clinical trials were made on the use of Urokinase but these were not large-scale studies, so it wasn't possible to establish the efficacy of Urokinase in the treatment of AIS. Although Urokinase has been widely used for thrombolysis in China for AIS, because of its cost and lack of significantly good clinical outcomes, it is no longer available for use in most countries for the treatment of AIS.

Alteplase (Activase rtPA)

Alteplase is a recombinant form of human tPA. It is fibrin-specific and has a plasma half-life of 4-6 minutes and therefore is usually administered as an intravenous bolus followed by an infusion [14, 16]. Physicochemical characteristics: Alteplase is a glycoprotein enzyme (serine protease) containing 527 amino acids, it is produced by recombinant DNA technology utilizing the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from human melanoma cell line[17, 18]. Alteplase is more clot-selective than the other thrombolytic agents, binding more efficiently to the fibrin-plasminogen complex within a clot than to circulating plasminogen [17]. Alteplase may be readministered as necessary, it is not antigenic and is almost never associated with any allergic manifestations. Alteplase is the only drug approved by the FDA for use in AIS with a well-established time of symptom onset (within 3 hours) [14, 19].

The European Cooperative Acute Stroke Study (ECASS III) tested the efficacy and safety of Alteplase administered between 3 and 4.5 hours after the onset of stroke symptoms and documented a favorable outcome at 90 days in 52.4% of treated patients and in 45.2% in controls [20]. Symptomatic intracranial hemorrhage was reported in 2.4% of the intravenous tPA-treated group and 0.2% of the control group. In 2009, The American Heart Association and the American Stroke Association published a scientific advisory statement recommending its use 3 to 4.5 hours from AIS symptom onset for eligible patients without contraindications [14, 21]. The recommended dose of Alteplase for AIS is 0.9 mg/kg (maximum, 90 mg) infused over 60 minutes, with 10% of the total dose administered as an initial intravenuos bolus over 1 minute[19, 22].

Alteplase is a safe and effective treatment for carefully selected stroke patients presenting within 3 hours of symptom onset and current evidence shows that it is safe if administered within 4.5 hours of the onset of AIS symptoms [23, 24].

The benefit is higher if Alteplase is given earlier, this enhanced benefit is attributed to rescuing the area of ischemic penumbra. Although risks associated with its use with inappropriate patients, do not outweigh the benefits [14].

Pro-Urokinase

Pro-Urokinase is a new fibrinolytic agent currently

undergoing clinical trials for a variety of indications. It is a relatively inactive precursor that must be converted to Urokinase before it becomes active in vivo. It has been studied in the settings of AMI, AIS, and peripheral arterial occlusion. Pro-Urokinase is relatively fibrin-specific, a feature explained by preferential activation of fibrin-bound plasminogen found in a thrombus over the free plasminogen in flowing blood, it has a half-life of about 7-9 minutes [9]. Pro-Urokinase has a greater ability to dissolve thrombus and is safer to use than Urokinase.

In spite of the good clinical results Pro-Urokinase is yet to receive FDA approval for AIS treatment. The prolyse in acute cerebral thromboembolism II (PROACT II) trial compared the efficacy of intra-arterial pro-urokinase treatment with intravenous heparin in middle cerebral artery (MCA) occlusion. Recanalization rate was 66% in the pro-urokinase, and 18% in the heparin group. Treatment with IA r-proUK within 6 hours of the onset of AIS caused by MCA occlusion significantly improved clinical outcome at 90 days.

Reteplase (Retavase)

Reteplase is a genetically engineered, smaller derivative of recombinant tPA that has increased potency and is faster acting than rtPA. It is usually administered as intravenous bolus injections. It is used for Acute Myocardial Infarction and Pulmonary Embolism [16]. Reteplase is a third-generation recombinant tissue-type plasminogen activator that seems to work more rapidly and to have a lower bleeding risk than Alteplase. In the treatment of AMI it is administered as 2 boluses of 10 U given 30 minutes apart, with each bolus administered over 2 minutes, and half-life is 13-16 minutes in length. Reteplase has a higher resistance to plasminogen activator inhibitor-1, clinical trials testing its efficacy in AIS patients were limited [14, 25]. V. Misra et al. investigated the safety of high intra-arterial doses of Reteplase for AIS. They concluded that there is no correlation between the dose of intra-arterial Reteplase and the development of symptomatic intracranial hemorrhage [26]. Although Reteplase has not been extensively studied in the treatment of ischemic stroke, the efficacy and the safety has to be proven with larger trials [26-29].

Tenecteplase

Tenecteplase (TNK-tPA) has a longer half-life and greater binding affinity for fibrin than rtPA. Because of its longer half-life, it can be administered by intravenous bolus. However it is only approved for use in Acute Myocardial Infarction [15]. It is produced by recombinant DNA technology using Chinese hamster ovary cells. Its mechanism of action is similar to that of Alteplase [14]. Tenecteplase is a 527-amino-acid glycoprotein (GP) that sustained several modifications in amino acid molecules. These modifications consist of substitution of asparagine for threonine 103 and glutamine for asparagine 117, as well as a tetra-alanine substitution at amino acids 296-299 in the protease domain [14]. Tenecteplase has a half-life ranging initially from 20-24 minutes to 130 minutes for final clearance, mostly through liver metabolism [30]. Tenecteplase is administered in a 30-50 mg intravenous bolus over 5 seconds. The dosage is calculated on the basis of the patient's weight [14]. Tenecteplase also has a greater resistance to plasminogen activator inhibitor-1. M.W. Parsons et al. did a prospective study on two groups, one with 15 patients using Tenecteplase 0.1mg/kg from 3h to 6h after stroke onset and the other one with 35 patients using Alteplase 0.9 mg/kg intravenous within 3h after stroke onset. A reperfusion of 74% was seen in the Tenecteplase group and 10 of the 15 patients had major neurologic improvement at 24 hours.

Thrombolytic inclusion/exclusion criteria

In 1991, about 500 000 Americans had a stroke (about 400 000 were ischemic stroke) and in 1994 the annual health care expenses for stroke were estimate $ 20 billion [31]. After the discovery that the thrombolytic therapy could limit brain injury more studies were made. In 1995 NINDS published a Recombinant Tissue Plasminogen Activator (rt-PA) Stroke Trial it was the largest with Part 1 (in which 291 patients were enrolled) and Part 2 (in which 333 patients were enrolled). Treatment within three hours of the onset of ischemic stroke improved clinical outcome at three months [23].

It is necessary that the inclusion/exclusion criteria for thrombolytic therapy is properly followed for the safety of the patients. Thrombolytic therapy is the new modality to treat AIS and can only be used after discussing the risks/benefits of the treatment with the patient and/or the family and their approval. In May 2009, and again in March 2013, the AHA/ASA guidelines for the administration of rt-PA following acute stroke were revised to expand the window of treatment from 3 hours to 4.5 hours to provide more patients with an opportunity to receive the benefits from this effective therapy [, 20, 31]. Table 1 lists the inclusion and exclusion criteria for intravenous tPA for AIS used on the National Institute for Neurological Disorders (NINDS), the European Cooperative Acute Stroke Study (ECASS III) trial and the New England Journal Of Medicine [20, 23, 32].

Thrombolytic side effects

After administering thrombolytic treatment a rigorous control of neurologic status is required, any new signs such as severe headache, decreased level of consciousness, a sudden increase of blood pressure, nausea, vomiting or an increase of NIHSS score, a CT scan or MRI, Type and cross-match, PTT/INR, platelets, and serum fibrinogen levels should be performed. The major risks of thrombolysis are intracranial hemorrhage, systemic hemorrhage, immunologic complications, hypotension, angioedema, swelling of the ischemic tissue and myocardial rupture [33, 34, 36].

Intracerebral hemorrhage: The hemorrhagic complications of thrombolysis occur most commonly in 24 hours after starting the therapy [33]. Around 6% of patients have intracerebral hemorrhage associated with early worsening of physical condition [37]. Symptomatic intracerebral hemorrhage has a 45% mortality rate in patients who have received thrombolytic. An immediate discontinue infusion is required.

Systemic bleeding: Minor bleeding is common after thrombolytic administration. In case of minor bleeding, there is no need to stop the infusion, but simply monitor for further or more extensive bleedings, a systemic bleeding can be seen by oozing at intravenous sites, ecchymosis, and bleeding gums[34].

Angioedema

Mild orolingual angioedema is seen in 1%-5% of patients receiving intravenous TPA [1, 2]. Typically, it is mild and transient, and affects the contralateral side from the hemisphere of ischemic injury [34]. Severe angioedema after TPA is a rare occurrence. If patients becomes stridorous, infusion should be stopped immediately [33].

Conclusion

Thrombolytic therapy has been recently the subject of intense investigation. In the past few years, nine randomized, placebo-controlled trials have been reported using intravenous recombinant tissue plasminogen activator (tPA), streptokinase, or intra-arterial recombinant pro-Urokinase (rpro-UK) [23, 34, 38-47]. Other intravenously administered thrombolytic agents, including Reteplase, Urokinase, and Staphylokinase, might have been considered for treatment of patients with AIS. However none of them were extensively tested [34, 47]. Intravenous thrombolysis remains the only proven medical treatment for reducing the disability caused by AIS [30, 48]. Thrombolytic treatment within three hours of stroke is more effective in reducing mortality or physical inability (OR 0.66, 95% CI 0.56 to 0.79), trials testing rt-PA revealed a significant reduction in mortality or dependency (OR 0.65, 95% CI 0.54 to 0.80, P < 0.0001) [49]. Randomized trials of different agents, doses and routes of thrombolysis in AIS were compared and showed poor evidence to determinate whether one agent is better than another or which method of administration is the best, currently intravenous rt-PA at 0.9mg/kg seems to provide best outcome[50] .

Table 1: The inclusion and exclusion criteria for intravenous tPA for Acute Ischemic Stroke

The New England Journal of Medicine	NINDS Criteria	ECASS III Criteria
Inclusion: **1.** Acute Ischemic Stroke **2.** Age, 18 to 80 years **3.** Onset of stroke symptoms 3 to 4. 5 hours before initiation of study-drug administration **4.** Stroke symptoms present for at least 30 minutes with no significant improvement before treatment **Exclusion**: **1 .**Intracranial hemorrhage **2.** Time of symptom onset unknown **3.** Symptoms rapidly improving or only minor before start of infusion **4.** Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques* **5.** Seizure at the onset of stroke **6.** Stroke or serious head trauma within the previous 3 months **7.** Combination of previous stroke and diabetes mellitus **8.** Administration of heparin within the 48 hours preceding the onset of	**Inclusion:** **1.** Acute Ischemic Stroke with clearly defined time of onset (who could be treated <3 hours of symptom onset) **2.** Measurable deficit on the NIH stroke scale 3.Baseline brain CT scan that showed no evidence of hemorrhage. **Exclusion:*** **1.** Another stroke or serious head injury within the preceding 3 months **2.** Major surgery within prior 14 days **3.** History of intracranial hemorrhage **4.** Systolic BP >185 mm Hg or diastolic BP >100 mm Hg **5.** Rapidly improving or minor symptoms **6.** Symptoms suggestive of subarachnoid hemorrhage Gastrointestinal or genitourinary	**Inclusion**: **1.** Acute Ischemic Stroke with a clearly defined time of onset (who could be treated between 3-4. 5 hours from symptom onset) **2.** Age 18-80 years Stroke symptoms present for at least 30 minutes without significant improvement prior to treatment. **3.** Baseline brain imaging that showed no evidence of hemorrhage. **Exclusion:*** **1.** Same as NINDS plus the following additional criteria: **2.** Age >80 years **3.** Severe stroke (NIHSS >25) or by appropriate imaging techniques (defined as >1/3 of the middle cerebral artery territory) **4.** Combination of previous stroke and diabetes mellitus **5.** Any oral anticoagulant use (regardless of INR or PT).

stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range **9.** Platelet count of less than 100, 000 per cubic millimeter **10.** Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits **11.** Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter **12.** Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal **13.** Oral anticoagulant treatment **14.** Major surgery or severe trauma within the previous 3 months **15.** Other major disorders associated with an increased risk of bleeding.	hemorrhage within the previous 21 days **7.** Arterial puncture at a noncompressible site within the previous 7 days **8.** Seizure at onset of stroke **9.** Use of anticoagulation: patients receiving heparin within the 48 hours preceding the onset of stroke who have an elevated PTT, patients with a PT >15 seconds (or INR >1.6), patients with a platelet count <100, 000 Glucose level of <50 mg/dL or >400 mg/dL.	

* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

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