

Pharmacotherapy Updates of Recombinant Tissue Plasminogen Activator (r-TPA) in Acute Ischemic Stroke

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Abstract

Context: According to published articles, thrombosis is the main reason for death all over of the world. With stroke time missing is brain missing, therefore, the FDA-approved drug r-TPA, could be administered as initial IV bolus in less than 3 - 4.5 hours from onset of Acute Ischemic Stroke (AIS). The aim of this review was to provide updated pharmacotherapy related to r-TPA in AIS.

Evidence Acquisition: Searches for associated published articles were conducted in major databases until September 2015. The main terms used in the search were a combination of words and phrases such as ischemic stroke and tissue plasminogen activator.

Results: Age, time of onset, systolic blood pressure, diabetes, stroke severity, co-morbidities and premorbid medical situation, stroke scale according to national institute of health and outcomes related to CT (head, angiogram and perfusion) were considered when determining successful treatment by endovascular thrombectomy. According to the 2015 guidelines, strategies related to successful pharmacotherapy management should be based on class I evidence-care on a stroke unit, IV-r-TPA within 3 - 4.5 hours of stroke onset, aspirin commenced within 48 hours of stroke onset, and decompressive craniectomy for supratentorial malignant hemispheric cerebral infarction. Hemorrhagic stroke (intraparenchymal, subarachnoid, intraventricular, intracerebral such as orolingual angioedema), hematoma (epidural and subdural) and head trauma are the absolute contraindications related to r-TPA prescription.

Conclusions: Due to considerable inter- and intra- heterogeneity among studies performed by other centers such as differences in study project, background, and population features, determining a pharmacotherapy model based on Safe Implementation of Treatments in stroke or SITS seem advantageous.

Keywords: TPA, Ischemic, Stroke, Pharmacotherapy

1. Context

Stroke, one of the most devastating cerebrovascular and neurological diseases, is a serious life-threatening condition and a leading cause of long-term adult disability and brain damage, either directly or by secondary complications. A great proportion of patients are those with acute ischemic stroke (AIS). The most effective managements for stroke are time dependent such as reperfusion with tissue-type plasminogen activator (tPA); thus, improving tissue oxygenation with hyperbaric oxygen therapy that has been reflected as a rational and potential significant combination therapy (1, 2). Tissue-type plasminogen activator is a protein (serine protease) elaborate in the interruption of blood clots. If tPA is manufactured by recombinant biotechnology methods then it is called recombinant tissue plasminogen activator (rtPA). Intravenous rtPA was first approved for pharmacotherapy management of AIS in the United States in 1996. Thrombolytic therapy has been established to be effective in acute is-

chemic stroke treatment and shown to improve long-term functional outcomes (3). Published literature suggested significant change in large vessel occlusive stroke via extensive use of thrombolysis followed by endovascular clot abolition pharmacotherapy. Within endothelial cells, that line the blood vessels, rtPA, catalyzes the conversion of plasminogen to plasmin. However, in hemorrhagic stroke and head trauma, tPA is contraindicated, yet to treat embolic or thrombotic stroke, tPA (like alteplase, reteplase, and tenecteplase) could be prescribed. Important factors related to endovascular thrombectomy could include age, time of commencement, premorbid clinical condition, co-morbidities, and imaging criterion including computed tomography (CT) head, CT angiogram and CT perfusion. Plasmin is the major enzyme for clot breakdown. In order to breakdown blood clots in other conditions such as pulmonary embolism and acute myocardial infarction, tPA also could be prescribed systemically. In events related to peripheral arterial thrombi and thrombi in the proximal deep veins of the leg, it could be administered through

an arterial catheter straight to the site of occlusion (4-7). There has also been a report on patients with frostbite indicating that those who are managed with tPA had less amputation than those who were not treated (8). Table 1 shows the pharmacotherapy properties of tPA. Feared complications include symptomatic intracerebral hemorrhage and orolingual angioedema (3). Hemorrhagic complications such as subarachnoid hemorrhage have been reported (4-9). In order to achieve appropriate tPA-strategies in patients with AIS, available therapeutic guidelines that support the best preliminary evidenced-based tPA management have been considered.

Table 1. Pharmacotherapy Properties of Tissue Plasminogen Activator (tPA)¹⁻³⁰

Variable	Pharmacotherapy Properties
Could be considered	As thrombolytic drug category
Dose	
0.9 mg/kg	Max, 90
10% of dose	As initial IV bolus
Reminder	infused over one hour, for maximum effectiveness
To be used	< 3 hours of symptoms start
To be ruled out	hemorrhage
Indication	Embolic stroke
	Thrombotic stroke
	Pulmonary embolism
	Acute Myocardial Infarction
Contra-indication	Symptomatic intracerebral hemorrhage as well as orolingual angioedema
	Hemorrhagic stroke; intraparenchymal hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, epidural hematoma, subdural hematoma, or hemorrhagic conversion of infarction
	Head trauma

2. Evidence Acquisition

The purpose of this study was to recognize approaches for pharmacotherapy-updated strategy of tissue plasminogen activator in patients with acute ischemic stroke. Searches for relevant articles were conducted in major databases such as; cochrane library plus, medline (PubMed), Embase, web of science (Web of Knowledge) and Scopus. Manuscripts from relevant investigations and review articles were selected. The main terms used in the search were a combination of MeSH terms (e.g. 'Ischemic Stroke', 'Tissue plasminogen activator'). Articles published before September 2015 were retrieved. Different consequences of attention were recognized in the literature and

then classified for taking into account for their clinical relevance.

3. Results

When oxygen-rich blood flowing to the brain is restricted either by a blood clot or other hindrance, ischemic stroke (IS) could occur. In these events pharmacotherapy based on substances that prevent blood from clotting by suppressing the synthesis of function of various clotting factors seem to be beneficial. However, the typical precise reperfusion remedy in AIS in both anterior and posterior cerebral flow is intravenous thrombolysis but studies suggest that posterior circulation stroke is associated with a lower risk of intracranial hemorrhage than anterior circulation (10). The FDA-approved the drug rTPA (0.9 mg/kg; max 90 mg) at the 10% dose, as initial IV bolus, with the remainder infused over one hour; for maximum efficacy, to be used < 3 hours of symptoms onset, in hemorrhage to be ruled out could be considered as thrombolytic drug category. A study on a 57 year-old-lady, regarding acute stent occlusion through emergent neuroendovascular revascularization after IV rtPA management, suggested that Intra-arterial (IA) eptifibatide could be considered as an operative decision (11).

Whereas Wardlaw et al. (12), in year 2012 stated that rtPA given within six hours of a stroke considerably augmented the chances of being alive and independent at final follow-up, mainly in those treated within three hours, yet an article published by Newman, in 2013, suggested beneficial early administration within 0 - 3 hours, and harmful later administration of 3 - 4.5 and again beneficial administration of 4.5 - 6 hours (9). In the first week of rtPA-therapy intracranial hemorrhage was reported to be the most common cause of mortality (12). Kirkman et al. (6), in 2015, reported that challenges in the treatment of acute ischemic stroke should be categorized based on introduction of numerous interferences reinforced by; 1) class I evidence-care on a stroke unit, 2) intravenous tissue plasminogen activator within 4.5 hours of stroke onset, 3) aspirin commenced within 48 hours of stroke onset, 4) and decompressive craniectomy for supratentorial malignant hemispheric cerebral infarction. There is also new evidence demonstrating benefits of endovascular therapy on functional consequences in those with anterior circulation stroke. In addition, the importance of careful management of key general physiological variables such as oxygenation, blood pressure, temperature, and serum glucose has been demonstrated (6). Intraventricular hemorrhage (IVH) is thought to result in poor outcome in patients with aneurysmal subarachnoid hemorrhage (SAH).

Intraventricular rtPA has no significant efficacy on long-term functional recovery after aneurysmal SAH with IVH. However, high dosage of rtPA might decrease the incidence of angiographic vasospasm.

Shirakawa et al. (13), in 2015 reported that despite the growing use of intravenous rtPA-therapy, a large number of patients are not suitable for treatment. The number of endovascular treatments for acute ischemic stroke is increasing each year. This treatment provides higher recanalization rates for occluded vessels but may lead to hemorrhagic complications such as subarachnoid hemorrhage. Results were announced for three randomized controlled trials in 2013, with all failing to show the superiority of endovascular treatment. For patients with progressive stroke, due to anterior circulation major vessel occlusion, the feasible treatment is microsurgical revascularization (14).

Regarding the prescription of non-agenarians patients with AIS, previous reports confirm that although a small fraction of these patients might be treated with rtPA-therapy (similar as octogenarians), yet most of them have poor 30-day functional outcome or die (15-17).

4. Conclusions

Since 2003 to 2011, a doubling rate for rtPA-therapy in the united states has been reported with an attentive concern related to patient's eligibility and prescription-management within three hours after onset of symptoms (15).

Up dated recommendations indicated IV-rtPA to vigilantly selected patients, those could be treated within 4.5 hours of AIS. Due to doubt about the time of onset on a rationally large population of patients, those with neurologic signs that are revealed upon awakening-up stroke are usually not given rtPA. Initial studies suggest that patients with wake-up stroke could be treated within 4.5 hours of detection. These groups may answer equally to patients with a recognized time of onset (18).

According to a recently published article by Spokoyny et al. (19), to confirm ideal supervision of patients with AIS, the precise documentation of last known normal time seems to be critical. Due to the time sensitivity of thrombolytic therapy, there is need for training in the determination and alteration of the actual time of stroke onset. Evidence-based study of rtPA associated with twelve different studies noted that two of these trials presented advantage for patients, four investigations exhibited injury and had to be blocked before the finishing point, and the remaining displayed neither value nor destruction. They suggested beneficial early administration within three hours, harmful later administration of 3 to 4.5 or 4.5 to

6 hours and again beneficial administration of 4.5 to 6 hours (9). However, to reach reperfusion in patients with AIS, injury related to blood-brain barrier or hemorrhagic transformation (HT) that could be a serious complication of IV-rtPA should be always kept in mind yet the study suggests that the increased risk of HT is not dependent on the reperfusion status (20). Previous studies have shown that rtPA interacts with fibrinogen alpha-chain (21), Low density lipoprotein receptor-related protein-1 (LRP1) (22, 23) and neuroserpin or serpinii gene (24). Evaluations related to the effects of hyperglycemia in thrombolysis ischemic stroke patients on recanalization rate and clinical outcome showed that hyperglycemia might be associated with low rate of complete recanalization and poor clinical outcome in IV-rtPA-treated patients (25). The tPA is quickly inactivated by endogenous plasminogen activators inhibitor-1 (PAI-1) (26). Trials based on the national institute of neurological disorders and Stroke consented that most of the contraindications to the administration of IV-rtPA originated as exclusion criteria. It has been suggested that application of relaxed exclusion criteria might increase the IV thrombolysis rate by up to 20% with similar consequences to thrombolysis with more conservative criteria. On brain imaging, a hemorrhage that includes intraparenchymal, subarachnoid, intraventricular and epidural or subdural hematoma, or hemorrhagic conversion of infarction is an absolute contraindication to prescribing IV-rtPA (27).

A published report confirmed that in the safe implementation of treatments in stroke (SITS) registry, higher systolic blood pressure (SBP) after lysis was individually related to worse consequences and an increased risk of intracranial hemorrhage (ICH). Thrombolysis-associated ICH generally occurs at the location of ischemic brain tissue though can present at a distant, unrelated place. Conventionally, the risk of remote cerebral hemorrhage post thrombolysis has been reported as happening in around 1.3% - 3.7% of patients (28). The recent published SITS investigation, which included 45,079 patients treated with IV r-tPA, discovered that remote parenchymal hematomas made up one-third of all parenchymal hematomas after IV thrombolysis (3).

Finally, for successful approach that engaged to treatment effect modifier, realizing a well-balanced pharmacotherapy model for r-TPA, such as onset to proper treatment time, advanced examination based on appropriate-registry system (29, 30), seem to be valuable.

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References

- Weaver J, Liu KJ. Does normobaric hyperoxia increase oxidative stress in acute ischemic stroke? A critical review of the literature. *Med Gas Res.* 2015;5:11. doi: [10.1186/s13618-015-0032-4](https://doi.org/10.1186/s13618-015-0032-4). [PubMed: 26306184].
- Michalski D, Küppers-Tiedt L, Weise C, Laiguel F, Härtig W, Raviolo M, et al. Long-term functional and neurological outcome after simultaneous treatment with tissue-plasminogen activator and hyperbaric oxygen in early phase of embolic stroke in rats. *Brain Res.* 2009;1303:161-8. doi: [10.1016/j.brainres.2009.09.038](https://doi.org/10.1016/j.brainres.2009.09.038).
- O'Carroll CB, Aguilar MI. Management of postthrombolysis hemorrhagic and orolingual angioedema complications. *Neurohospitalist.* 2015;5(3):133-41. doi: [10.1177/1941874415587680](https://doi.org/10.1177/1941874415587680).
- Paramasivam S. Current trends in the management of acute ischemic stroke. *Neurol India.* 2015;63(5):665-72. doi: [10.4103/0028-3886.166547](https://doi.org/10.4103/0028-3886.166547).
- Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. *Neurology.* 2013;80(1):21-8. doi: [10.1212/WNL.0b013e31827b1ace](https://doi.org/10.1212/WNL.0b013e31827b1ace). [PubMed: 23175723].
- Kirkman MA, Lambden S, Smith M. Challenges in the Anesthetic and Intensive Care Management of Acute Ischemic Stroke. *J Neurosurg Anesthesiol.* 2015. doi: [10.1097/ANA.0000000000000225](https://doi.org/10.1097/ANA.0000000000000225). [PubMed: 26368664].
- Shi L, Xu L, Shi L, Brandon D, Chen S, Zhang J. Intraventricular Recombinant Tissue Plasminogen Activator in Treatment of Aneurysmal Intraventricular Hemorrhage: A Meta-Analysis. *Curr Drug Targets.* 2015 [PubMed: 26343113].
- Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma.* 2005;59(6):1350-4. [PubMed: 16394908] discussion 1354-5.
- Newman DH, Shreves AE. Thrombolysis in acute ischaemic stroke. *Lancet.* 2012;380(9847):1053-4. doi: [10.1016/S0140-6736\(12\)61593-1](https://doi.org/10.1016/S0140-6736(12)61593-1). [PubMed: 22998705] author reply 1054-5.
- Dornak T, Kral M, Hazlinger M, Herzig R, Veverka T, Burval S, et al. Posterior vs. anterior circulation infarction: demography, outcomes, and frequency of hemorrhage after thrombolysis. *Int J Stroke.* 2015;10(8):1224-8. doi: [10.1111/ijis.12626](https://doi.org/10.1111/ijis.12626).
- Sorkin GC, Dumont TM, Mokin M, Eller JL, Natarajan SK, Levy EI, et al. Hyperacute carotid stent thrombosis during emergent revascularization treated with intraarterial eptifibatid after systemic administration of recombinant tissue plasminogen activator. *J Vasc Interv Neurol.* 2015;8(3):50-5.
- Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet.* 2012;379(9834):2364-72. doi: [10.1016/S0140-6736\(12\)60738-7](https://doi.org/10.1016/S0140-6736(12)60738-7). [PubMed: 22632907].
- Shirakawa M, Yoshimura S, Yamada K, Uchida K, Shindou S. Endovascular Treatment for Acute Ischemic Stroke: Considerations from Recent Randomized Trials. *Interv Neurol.* 2015;3(3-4):115-21. doi: [10.1159/000375540](https://doi.org/10.1159/000375540). [PubMed: 26279657].
- Sugiyama T, Kazumata K, Asaoka K, Osanai T, Shimbo D, Uchida K, et al. Reappraisal of Microsurgical Revascularization for Anterior Circulation Ischemia in Patients with Progressive Stroke. *World Neurosurg.* 2015;84(6):1579-88. doi: [10.1016/j.wneu.2015.07.053](https://doi.org/10.1016/j.wneu.2015.07.053).
- Bankhead C, Agus ZS. Clot-busting drugs used more often in stroke Medpage Today; 2013. Available from: <http://www.medpagetoday.com/Cardiology/Stroke/41156>.
- Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S, et al. Temporal Trends in Patient Characteristics and Treatment With Intravenous Thrombolysis Among Acute Ischemic Stroke Patients at Get With the Guidelines-Stroke Hospitals. *Circ Cardiovasc Qual Outcomes.* 2013. doi: [10.1161/CIRCOUTCOMES.111.000095](https://doi.org/10.1161/CIRCOUTCOMES.111.000095). [PubMed: 23963655].
- Mateen FJ, Nasser M, Spencer BR, Freeman WD, Shuaib A, Demaerschalk BM, et al. Outcomes of intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 90 years or older. *Mayo Clin Proc.* 2009;84(4):334-8. doi: [10.1016/S0025-6196\(11\)60542-9](https://doi.org/10.1016/S0025-6196(11)60542-9). [PubMed: 19339651].
- Adams HJ. IV thrombolysis for treatment of patients with stroke upon awakening: Yes? No?. *Neurol Clin Pract.* 2015;5(4):296-301. doi: [10.1212/CPJ.0000000000000152](https://doi.org/10.1212/CPJ.0000000000000152). [PubMed: 26336630].
- Spokoyny I, Raman R, Ernstrom K, Kim AJ, Meyer BC, Karanjia NP. Accuracy of First Recorded "Last Known Normal" Times of Stroke Code Patients. *J Stroke Cerebrovasc Dis.* 2015;24(11):2467-73. doi: [10.1016/j.jstrokecerebrovasdis.2015.04.041](https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.04.041). [PubMed: 26341734].
- Horsch AD, Dankbaar JW, van der Graaf Y, Niesten JM, van Seeters T, van der Schaaf IC, et al. Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. *Neuroradiology.* 2015;57(12):1219-25. doi: [10.1007/s00234-015-1577-6](https://doi.org/10.1007/s00234-015-1577-6). [PubMed: 26337766].
- Tsurupa G, Medved L. Identification and characterization of novel tPA- and plasminogen-binding sites within fibrin(ogen) alpha C-domains. *Biochemistry.* 2001;40(3):801-8. [PubMed: 11170397].
- Orth K, Madison EL, Gething MJ, Sambrook JF, Herz J. Complexes of tissue-type plasminogen activator and its serpin inhibitor plasminogen-activator inhibitor type 1 are internalized by means of the low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor. *Proc Natl Acad Sci U S A.* 1992;89(16):7422-6. [PubMed: 1502153].
- Parmar PK, Coates LC, Pearson JF, Hill RM, Birch NP. Neuroserpin regulates neurite outgrowth in nerve growth factor-treated PC12 cells. *J Neurochem.* 2002;82(6):1406-15. [PubMed: 12354288].
- Brimelow A. Safety review into stroke clot-buster drug alteplase. BBC News British broadcasting corporation; 2015. Available from: www.bbc.com/news/health.
- Saqqur M, Shuaib A, Alexandrov AV, Sebastian J, Khan K, Uchino K. The correlation between admission blood glucose and intravenous rt-PA-induced arterial recanalization in acute ischemic stroke: a multicentre TCD study. *Int J Stroke.* 2015;10(7):1087-92. doi: [10.1111/ijis.12517](https://doi.org/10.1111/ijis.12517).
- Gong L, Liu M, Zeng T, Shi X, Yuan C, Andreasen PA, et al. Crystal structure of the Michaelis complex between tissue-type plasminogen activator and plasminogen activators inhibitor-1. *J Biol Chem.* 2015;290(43):25795-804.
- Fugate JE, Rabinstein AA. Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic Stroke. *Neurohospitalist.* 2015;5(3):110-21. doi: [10.1177/1941874415578532](https://doi.org/10.1177/1941874415578532). [PubMed: 26288669].
- Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke.* 2009;40(7):2442-9. doi: [10.1161/STROKEAHA.109.548602](https://doi.org/10.1161/STROKEAHA.109.548602). [PubMed: 19461022].
- Tolou-Ghamari Z, Mortazavi M, Palizban AA, Najafi MR. The investigation of correlation between Iminoral concentration and neurotoxic levels after kidney transplantation. *Adv Biomed Res.* 2015;4. doi: [10.4103/2277-9175.151876](https://doi.org/10.4103/2277-9175.151876).
- Tolou-Ghamari Z, Zare M, Habibabadi JM, Najafi MR. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. *J Res Med Sci.* 2013;18(Suppl 1):S81-5. [PubMed: 23961295].