PROTOCOL FOR USE OF INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE
HARBORVIEW MEDICAL CENTER – UNIV. OF WASHINGTON MEDICAL CENTERS

Based on protocols from NINDS t-PA Stroke Study Group (NEJM 1995;33:1581-87), AAN Practice Advisory (Neurology 1996;47:835-839) and AHA Guidelines (Stroke 1996;27:1711-18, Stroke. 2005;36:916, Stroke 2007; 38:1655-1711, Stroke 2009;40;2945-8, Stroke 2013; 44: 870-947;Stroke 2015; 46:3020-3035; Stroke 2018; 49:e46-e99; Stroke 2019; 50:e344-e418; WAKE-UP and EXTEND trials).
Reviewed and updated July 2021

INCLUSION CRITERIA

- Age ≥ 18 years old
- Clinical diagnosis of ischemic stroke causing a disabling neurologic deficit
    - Ischemic stroke is defined as an event characterized by the sudden onset of an acute focal neurologic deficit presumed to be due to brain ischemia after CT excludes hemorrhage
- Onset of symptoms of ischemic stroke <u>within 3 hours</u> of the time to initiation of treatment with intravenous tissue plasminogen activator (t-PA).
- <u>3 - 4.5 hour time window</u> eligibility criteria for treatment are the same as those for persons treated at earlier time periods, WITH THE FOLLOWING ADDITIONAL CAUTIONARY CRITERIA:
    - Baseline NIHSS > 25
    - >80 years of age
    - Hx of both diabetes mellitus and prior stroke
    - Oral anticoagulant use
    - Evidence of ischemic injury involving >1/3 of the MCA territory
- Wake-up, unknown onset, and 4.5-9 hour window patients can be considered for IV tPA based on either the WAKE-UP trial or the EXTEND trial (all other inclusion and exclusion criteria apply; only WAKE-UP criteria are included in guidelines to date (with a moderate II-a level of recommendation), so informed consent is especially important and should be documented)
    - For the WAKE-UP trial, which applies to Wake-up and unknown onset patients (NEJM. 2018;379(7):611-622), a “Code Stroke MRI” must be done and show a diffusion abnormality without a corresponding FLAIR abnormality (this essentially suggests they are within 4.5 hours), then the patient can qualify for IV tPA treatment
    - For the EXTEND trial (NEJM. 2019;380(19):1795-1803), which applies to Wake-up or unknown onset patients if they are within 4.5-9 hours of clear last known well, or within 9 hours of mid-point of sleep period, a CTP can be performed and to qualify for IV tPA treatment the patient must meet criteria including:
        - Core (CBV < 30%) < 70 ml
        - (Penumbra (Tmax > 6 sec) – Core) (aka absolute difference) > 10 ml
        - Penumbra/Core (Mismatch Ratio) > 1.2

EXCLUSION CRITERIA

- CT scan with evidence of hemorrhage
- CT demonstrates extensive regions of clear hypoattenuation.
- Ischemic stroke within the previous 90 days
- History of severe head trauma within the previous 90 days
- Clinical presentation suggestive of subarachnoid hemorrhage, even if initial CT scan is normal
- Intracranial or intraspinal surgery within the past 90 days
- Hypertension with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg on repeated measures prior to starting tPA
- Active internal bleeding
- Hx of gastrointestinal malignancy or recent gastrointestinal or urinary tract hemorrhage within 21 days
- Acute hemorrhagic diathesis
    - Platelet count < 100,000/mm^3 *
    - Use of warfarin with prolonged PT > 15 sec, INR > 1.7 or aPTT >40 sec
    - Confirmed or suspected use of a direct thrombin inhibitor, such as dabigatran. ** *(Note: If the TT assay is normal (not elevated/prolonged), little or no dabigatran effect is present; the TT assay usually takes <10 minutes and is part of the Emergency Stroke Panel).*
    - Confirmed or suspected use of a direct factor Xa inhibitor, such as rivaroxaban or apixaban.** *(Note: there is a clear indicator of Xa inhibitor activity ordered as part of the ESP).*
    - Abnormal values in the Emergency Stroke Panel, which includes the TT, PT, and anti-Xa, should raise concerns.
    - Use of treatment dose heparin/LMWH in previous 24 hours
- Blood glucose < 50
- Arterial puncture at non-compressible site in the last 7 days
- Unruptured and unsecured large intracranial aneurysm (>10mm)
- Intracranial, intra-axial tumor (extra-axial tumors likely OK)
- Symptoms consistent with or known infective endocarditis
- Aortic Arch dissection

* = In patients without a history of thrombocytopenia, IV tPA can be started before platelet count returns, but should be discontinued if platelet count returns < 100,000/mm^3

** = IV tPA should not be used in a patient who has received FXa inhibitor < 48h

RELATIVE EXCLUSION CRITERIA

(Not absolute contraindications, may imply overall poorer prognosis, may increase risk of symptomatic hemorrhage, yet do not exclude the possibility of benefit from tPA therapy)

- Previous known non-traumatic intracranial hemorrhage (previously in exclusion criteria)
- Vascular malformation unless severe neurological deficits (ischemic risks outweigh those of ICH)
- Pregnancy; tPA has been given, with varying levels of success, risks to fetus and woman not clearly known, but may be considerable. Consult OB/Gyn immediately.
- Major extra-cranial surgery or trauma within 14 days
- Acute or recent MI within 3 months, depending on type of MI (though lower level evidence supports using tPA in these settings)
- Acute Pericarditis
- Abnormal aPTT, TT, or anti-Xa activity with unknown use of direct thrombin inhibitor or factor Xa inhibitor (may be false positive due to lupus anticoagulant, consider IV tPA if able to reliably confirm that patient is not taking one of these agents)
- Cerebral microbleeds: >10 known CMB may increase risk for ICH

If the patient has all of the inclusion criteria and none of the exclusion criteria, he or she is eligible for treatment with t-PA. If so, obtain informed consent and sign orders. If patient is not competent and there is no legally authorized representative, proceed without consent.

OTHER TREATMENTS

Antithrombotic therapies

Other antithrombotic therapies, including anticoagulants and antiplatelet agents, must be avoided for 24 hours following the administration of t-PA.

Hypertension

The protocol suggested by the NINDS t-PA Stroke Study Group will be followed. See standing orders for details.

Intracranial Hemorrhage

If neurologic deterioration, new headache, acute hypertension, nausea, vomiting or some combination of these problems, initiate the algorithm for suspected intracranial hemorrhage [see “possible hemorrhage post tpa protocol”]

Orolingual Angioedema (from 2019 AHA/ASA AIS guidelines)

Table 9. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

Class IIb, LOE C-EO
Maintain airway
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis post-IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.
Discontinue IV alteplase infusion and hold ACEIs
Administer IV methylprednisolone 125 mg
Administer IV diphenhydramine 50 mg
Administer ranitidine 50 mg IV or famotidine 20 mg IV
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACEI-related angioedema
Supportive care

ACEI indicates angiotensin-converting enzyme inhibitor; AIS, acute ischemic stroke: IV. intravenous: and LOE. Level of Evidence.