Jefferson
University Hospitals

CLINICAL PRACTICE GUIDELINE AND PROTOCOL

*GUIDELINE

*TITLE: Guidelines for the use of intravenous thrombolytic therapy on acute ischemic brain attack (stroke):

*CAMPUS(ES) AT WHICH ACTIVE (CC, JHN, MHD) All

*POSITION / TITLE OF DOCUMENT OWNER: Neurologist, Co-Director, Acute Stroke Unit

*PERSON IN THIS POSITION AT TIME OF CREATION: ***Dr. Carissia Pineda***

1. Development* (include all relevant information about the clinical situation being addressed, e.g. prevalence, practice variability, time sensitivity of clinical response, impact on patient safety and risk reduction, practice trends, etc):

Current guidelines for the management of patients with acute ischemic stroke, published by the American Heart Association Stroke Council, include specific recommendations for the administration of intravenous recombinant tissue plasminogen activator (rtPA). Despite its effectiveness in improving neurological outcomes, the majority of patients with ischemic stroke are not treated with rtPA because they arrive after the currently approved 3-hour time limit for administration of the medication.

The completion of a recent prospective study, the European Cooperative Acute Stroke Study (ECASS)-3, and a retrospective safety analysis, the Safe Implementation of Thrombolysis in Stroke – International Stroke Treatment Registry 3 to 4.5 hour study (SITS-ISTR 3 to 4.5 hour), have provided new data on rtPA treatment in the 3 to 4.5 hour window. Based on these studies and analysis of previous trials, the American Heart Association Stroke Council has released recommendations that rtPA may be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B)

2. Criteria for use* (the indications for applying this document – be specific, e.g. "all patients on mechanical ventilation", "all admissions from nursing homes"):

All patients age 18 to 80 years presenting with acute ischemic stroke, within 3 to 4.5 hours of onset of symptoms, and the absence of contraindications to thrombolytic therapy. Noted additional absolute contraindications are severe neurological deficit (NIHSS > 25), a history to previous stroke and diabetes mellitus, and current use of any oral anticoagulants regardless of INR.

3. Content

GUIDELINES FOR THE USE OF INTRAVENOUS THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC BRAIN ATTACK (STROKE) IN THE 0-3 HOUR WINDOW

I. CANDIDATES

A. Age 18 years or older.

B. Presenting with acute ischemic stroke within 3 hours of onset of symptoms

C. Absence of contraindications

D. Baseline CT scan of the brain shows no evidence of intracranial hemorrhage

E. A deficit measurable on the National Institutes of Health Stroke Scale (NIHSS)

F. Patient is not on a direct thrombin inhibitor, or a Factor Xa inhibitor (e.g dabigatran,rivaroxaban)

II. ABSOLUTE CONTRAINDICATIONS

Intravenous thrombolytic therapy in the following conditions is contraindicated because of an increased risk of bleeding, which could result in significant disability or death:

A. History of intracranial hemorrhage

B. Evidence of intracranial hemorrhage on pretreatment evaluation

C. Clinical presentation suggestive of subarachnoid hemorrhage, even if initial CT scan is normal

D. Recent previous stroke (3 months)

E. Recent intracranial or intraspinal surgery (3 months)

F. Recent serious head trauma (3 months)

G. Recent (within 14 days) major surgery (e.g., CABG, obstetrical delivery, organ biopsy)

H. Recent (within 21 days) GI or GU bleeding

I. Recent (within 7 days) arterial puncture at non-compressible site

J. Recent (within 7 days) lumbar puncture

K. Uncontrolled hypertension at time of treatment (systolic > 185 mmHg or diastolic > 110 mmHg), (see Section VI)

L. Active internal bleeding

M. Intracranial neoplasm, arteriovenous malformation or aneurysm

N. Bleeding diathesis including but not limited to:

1. Current use of warfarin or an International Normalized Ratio (INR) > 1.7 or a prothrombin time (PT) > 15 seconds
2. Administration of heparin within 48 hours preceding the onset of stroke and have an elevated activated thromboplastin time (aPTT) at presentation (> 1.5 to 2 times baseline)
3. Platelet count < 100,000/mm 3

III. RELATIVE CONTRAINDICATIONS

In the following conditions, the risks of intravenous thrombolytic therapy may be increased and should be weighed against the anticipated benefits:

A. Patients with severe neurological deficit (e.g., NIHSS > 22) at presentation.

B. Patients with major early infarct signs on CT scan (e.g., substantial edema, mass effect, midline shift, or hypodense areas)

C. Recent (within 7 days)arterial puncture of non-compressible vessels

D. Prior cerebrovascular disease

E. Recent (within 14 days) trauma

F. Recent (within 3 months) acute myocardial infarction

G. High likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)

H. Hemostatic defects including those secondary to severe hepatic or renal disease

I. Significant hepatic dysfunction

J. Pregnancy

K. Nursing mothers

L. Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions

M. Septic thrombophlebitis or occluded AV cannula at seriously infected site

N. Advanced age (e.g., over 75 years of age)

O. Patients currently receiving oral anticoagulants

P. Blood glucose < 50 or > 400 mg/dL

Q. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

R. Isolated, mild neurological deficits, such as ataxia alone, dysarthria alone, or minimal weakness

S. Rapidly improving or minor symptoms

PROCEDURE

A. Determine whether time is available to start treatment with alteplase (tPA) before 3 hours

B. Obtain history of symptoms, predisposing risk factors, prior stroke history, and possible contraindications to thrombolytic therapy (see Sections II and III)

C. Conduct a physical examination, obtain vital signs, and calculate a NIHSS score

D. Obtain ECG and appropriate laboratory studies

1. CBC, PT, PTT, INR, SMA-7, SMA-12, glucose. . If the suspicion for a stroke is high, and the patient does not have any known bleeding diathesis, hepatic disease, or is on any anticoagulation, IV tPA may be administered even without the results of the platelet count and INR.

2. CBC at 12 and 24 hours post-thrombolytic treatment

E. Obtain a non-contrast CT scan. MUST BE REVIEWED BY AN ATTENDING NEUROLOGIST, NEURORADIOLIGIST, AND/OR ATTENDING'S DESIGNEE

F. Explain the risks and benefits of thrombolytic therapy to the patient and/or family and document this on the chart

G. Start intravenous lines in both arms and initiate drug therapy (see Section V)

H. H. Monitor patient carefully, particularly the blood pressure (see Section VI for BP Management Guidelines)

I. After administering alteplase (tPA), monitor neurological status and vital signs q15m x 2hr, q30m x 6hr, and q1hr x 16hr

I. DRUG THERAPY

Alteplase (tPA, Activase®)

1. Dose: recommended dose is 0.9 mg/kg of body weight up to a maximum of 90mg. DO NOT EXCEED 90mg

2. Administration: Give 10% of calculated dose as IVPush over 1 minute. The remainder of the dose should be given by continuous infusion over 60 minutes. Do not filter. Flush line with 50mL of 0.9% Normal Saline after completion of infusion.

3. Preparation:

a. Contact 5 Gibbon Decentralized Pharmacy (215-955-7147) for preparation and dispensing of alteplase (tPA) pursuant to the physician's written/electronic order

b. Because alteplase (tPA) contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution must be used for IV administration within 8 hours after reconstitution when stored between 2-30°C (36 - 86°F)

Adjunctive Therapy

1. No anticoagulants or anti platelet agents should be given for 24 hours after treatment (e.g., heparin, warfarin, aspirin, clopidogrel)
2. If heparin or any other anticoagulant is indicated after 24 hours, perform a non-contrast CT to rule out any intracranial hemorrhage before starting the therapy

II. BLOOD PRESSURE MANAGEMENT GUIDELINES IN ACUTE ESCHEMIC STROKE

A. Refer to Hypertensive Emergency in Patients with Ischemic Stroke algorithm

B. Reductions of blood pressure in ischemic stroke patients should be gradual. Blood pressure should not be reduced to much below premorbid levels.

C. The primary agents indicated for control of elevated blood pressure are labetalol nicardipine.and clidepine

D. However, clinical judgment is recommended in determining the necessity, appropriate selection of medication, and degree to which hypertension therapy is treated.

E. Nitroprusside use is generally avoided in this patient population due to cerebral vasculature dilation and risk for increased intracranial pressure (ICP).

III. TREATMENT OF COMPLICATIONS OF THROMBOLYTIC THERAPY

A. If, in the clinical judgment of the treating physician, an intracranial hemorrhage is suspected, the administration of alteplase (tPA) should be immediately discontinued and an emergency noncontrast CT scan should be obtained.

B. Refer to Guidelines for the Management of Complications of Thrombolytic Therapy

GUIDELINES FOR THE USE OF INTRAVENOUS THROMBOLYTIC THERAPY ON ACUTE ISCHEMIC BRAIN ATTACK (STROKE): IN THE 3-4.5 HOUR WINDOW

IV. CANDIDATES

A. Age (18 years to 80 years). Use in younger or older patients may be considered, depending on co-morbidities

B. Presenting with acute ischemic stroke symptoms, or last seen normal within 3- 4.5 hours

C. Absence of contraindications

D. Baseline CT scan of the brain shows no evidence of intracranial hemorrhage

E. A deficit measurable on the National Institutes of Health Stroke Scale (NIHSS).

F. Patient is not on a direct thrombin inhibitor or Factor XA inhibitors (i.e. dabigatran, rivaroxaban)

V. ABSOLUTE CONTRAINDICATIONS

Intravenous thrombolytic therapy in the following conditions is contraindicated because of an increased risk of bleeding, which could result in significant disability or death:

A. Combination of previous stroke and diabetes mellitus

B. History of intracranial hemorrhage

C. Evidence of intracranial hemorrhage on pretreatment evaluation

D. Clinical presentation suggestive of subarachnoid hemorrhage, even if initial CT scan is normal

E. Recent previous stroke (3 months)

F. Recent intracranial or intraspinal surgery (3 months)

G. Recent serious head trauma (3 months)

H. Recent (within 14 days) major surgery (e.g., CABG, obstetrical delivery, organ biopsy)

I. Recent (within 21 days) GI or GU bleeding

J. Recent (7 days) arterial puncture at a non-compressible site

K. Recent lumbar puncture within 7 days

L. Uncontrolled hypertension at time of treatment (systolic > 185 mmHg or diastolic > II0 mmHg), or aggressive treatment required to reduce BP to specified limits (see Section VI)

M. Active internal bleeding

N. Intracranial neoplasm, arteriovenous malformation or aneurysm

O. Bleeding diathesis including but not limited to:

1. Current use of oral anticoagulants, regardless of their international normalized ration (INR)
2. Administration of heparin within 48 hours preceding the onset of stroke and have an elevated activated thromboplastin time (aPTT) at presentation (> 1.5 to 2 times baseline)
3. Platelet count < 100,000/mm3

P. Acute pericarditis/Subacute bacterial endocarditis

VI. RELATIVE CONTRAINDICATIONS

In the following conditions, the risks of intravenous thrombolytic therapy may be increased and should be weighed against the anticipated benefits:

A. Patients with severe neurological deficit (e.g. NIHSS > 22)

B. Patients with major early infarct signs on CT scan (e.g., substantial edema, mass effect, midline shift, or hypodense areas).

C. Recent (within 10 days) puncture of non- compressible vessels

D. Recent acute myocardial infarction (3 months)

E. Prior cerebrovascular disease

F. Recent (within 14 days) trauma

G. Hypertension: Systolic:::> 185 mmHg and/or diastolic:::> 110 mmHg

H. Seizure at the onset of stroke

I. High likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)

J. Hemostatic defects including those secondary to severe hepatic or renal disease

K. Significant hepatic dysfunction

L. Pregnancy

M. Nursing mothers

N. Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions

O. Septic thrombophlebitis or occluded AV cannula at seriously infected site

P. Blood glucose < 50 or > 400 mg/dL

Q. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of location

R. Isolated, mild neurological deficits, such as ataxia alone, dysarthria alone, or minimal weakness

S. Rapidly improving or minor symptom

IV. PROCEDURE

A. Determine whether time is available to start treatment with alteplase (tPA) before 4.5 hours

B. Obtain history of symptoms, predisposing risk factors, prior stroke history, and possible contraindications to thrombolytic therapy (see Sections II and III)

C. Conduct a physical examination, obtain vital signs, and calculate a NIHSS score

D. Obtain ECG and appropriate laboratory studies

1. CBC, PT, PTT, INR, SMA-7, SMA-I2, glucose. If the suspicion for a stroke is high, and the patient does not have any known bleeding diathesis, hepatic disease, or is on any anticoagulation, IV TPA may be administered even without the results of the platelet count and INR.

2. CBC at 12 and 24 hours post-thrombolytic treatment

E. Obtain a non-contrast CT scan. MUST BE REVIEWED BY AN ATTENDING NEUROLOGIST, NEURORADIOLIGIST, AND/OR ATTENDING'S DESIGNEE

F. Explain the risks and benefits of thrombolytic therapy to the patient and/or family and document this on the chart.

G. Start intravenous lines in both arms and initiate drug therapy (sec Section V)

H. Monitor patient carefully, particularly the blood pressure (sec Section VI for BP Management Guidelines)

I. After administering alteplace (tPA), monitor neurological status and vital signs q15min x 2hr, q30min x 6hr, and q1hr x 16hr

V. DRUG THERAPY

A. Alteplace (tPA, Activase®)

1. Dose: Recommended dose is 0.9 mg/kg of body weight up to a maximum of 90 mg. DO NOT EXCEED 90MG

2. Administration: Give 10% of calculated dose as IV Push over 1 minute. The remainder of the dose should be given by continuous infusion over 60 minutes. Do not filter. Flush line with 50mL of 0.9% Normal Saline after completion of infusion.

3. Preparation:

a. Contact 5 Gibbon Decentralized Pharmacy (215-955-7147) for preparation and dispensing of alteplase (tPA) pursuant to the physician's written/electronic order.

b. Because alteplase (tPA) contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution must be used for IV administration within 8 hours after reconstitution when stored between 2 - 30°C (36 - 86°F)

B. Adjunctive Therapy

1. No anticoagulants or anti platelet agents should be given for 24 hours after treatment (e.g., heparin, warfarin, aspirin, clopidogrel)
2. If heparin or any other anticoagulant is indicated after 24 hours, perform a non-contrast CT to rule out any intracranial hemorrhage before starting the therapy

VI. BLOOD PRESSURE MANAGEMENT GUIDELINES IN ACUTE ISCHEMIC STROKE

A. Refer to Hypertensive Emergency in Patients with Ischemic Stroke algorithm

B. Reductions of blood pressure in ischemic stroke patients should be gradual. Blood pressure should not be reduced to much below premorbid levels.

C. The primary agents indicated for control of elevated blood pressure are labetalol nicardipine, and clidepine. However, clinical judgment is recommended in determining the necessity, appropriate selection of medication, and degree to which hypertension therapy is treated.

D. Nitrooprusside use is generally avoided in this patient population due to cerebral vasculature dilation and risk for increased intracranial pressure (ICP).

VII. TREATMENT OF COMPLICATIONS OF THROMBOLYTIC THERAPY

A. If, in the clinical judgment of the treating physician, an intracranial hemorrhage is suspected, the administration of alteplase (tPA) should be immediately discontinued and an emergency noncontrast CT scan should be obtained.

B. Refer to Guidelines for the Management of Complications of Thrombolytic Therapy (below)

GUIDELINES FOR THE MANAGEMENT OF COMPLICATIONS OF THROMBOLYTIC THERAPY

Upon selection of the patient for thrombolytic therapy, treatment is initiated immediately and the patient must be closely observed for bleeding. The hematocrit is evaluated every 8 to 12 hours during the infusion of thrombolytic therapy. If there is a reduction of greater than 2%, a thorough search for bleeding site should be initiated. The following are guidelines for the management of bleeding complications.

A. Minor Bleeding

1. A void excessive phlebotomy, arterial punctures, or IM injections.
2. Minimize the use of arterial or venous catheters.

3. Observe potential bleeding sites such as arterial or venous, catheter punctures and wounds.
4. Apply prolonged manual pressure (> 15 min) to sites until bleeding stops.

B. Major Bleeding

1. Discontinue therapy
2. Fresh frozen plasma (FFP)

a) 2 units, I.V., every 6 to 8 hours

b) Reassess patient and repeat as above

3. Cryoprecipitate

    a) 10 units I.V.

    b) Reassess patient and repeat as above

C. Emergency (Life Threatening)

1. Fresh frozen plasma

    a) 2 units, I.V., every 6 to 8 hours

    b) Reassess patient, if bleeding continues, give antifibrinolytic agent

2. Cryoprecipitate

    a) 10 units, I.V.

    b) Reassess patient, if bleeding continues repeat dose and give FFP

3. Antifibrinolytic Therapy

    a) E-aminocaproic acid 5gm , I.V. loading, then 0.5g to 1gm/hr for 24 hours

4. If bleeding continues despite the use of the above agents then 10 units of platelets should be administered I.V.

4. Education plan*

JOB TITLE OF PERSON RESPONSIBLE FOR EDUCATION PLAN: Neurologist; Co-Director of the Acute Stroke Unit

CURRENT PERSON IN THIS ROLE: ***Carissa Pineda, MD***

Content will be placed on the Continuing Medical Education page of the hospital intranet, along with existing supporting documents and instructional presentations related to stroke. Residents will be directed to this material at the beginning of rotations through all patient care units on which a component of stroke care might reasonable be delivered. Content knowledge will be evaluated by the medical director of each unit as part of residents' performance reviews.

References to this material will also be incorporated into the alteplase for stroke JeffChart orderset.

5. Review and approval

A

REQUIRED	ENTITY	DATE	APPROVED
X	**Plrnrmacv & Theraoeutics Committee**	**2/5/2013**	Y
	Review by CPIC		
X	**Medical Executive Committee**	**1/14/2013**	Y

References

Jauch EC,Saver .IL,Adams HP, et al. Guidelines for early management of patients with acute ischemic stroke. Stroke 2013 ;44

- del Zoppo GJ, Saver JL, Jauch EC, et al. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. *Stroke* 2009 May Epub.
- Hacke W, Kaste M, Bluhmki E, et al. (ECASS Investigators) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *NE.JM* 2008;359:1317-29.
- Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase 3-4.5h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008;372:1303-09.
- Activase® (Alteplase) [package insert]. South San Francisco (CA): Genetech, Inc.; 2005.

6. Other information of importance

7. Measurement and outcomes assessment* - what parameter(s) will be followed to monitor use and effect of this document'?

Set Measure	Disease Specific Care Performance Measure Name
Stroke-4	Tissue Plasminogen Activator (t-PA) Considered

APPROVED BY:

Carissa Pineda, MD
Co-Director, Acute Stroke Unit

(SIGNATURE ON FILE)

Geno J. Merli, MD, FACP
Sr. Vice President & Chief Medical Officer

DATE OF APPROVAL: 9/14/2009

REVISION DATES: 2/5/2013