

Guidelines for the use of IV recombinant tissue plasminogen activator (rt-PA), Endovascular Thrombectomy (EVT), or rt-PA+EVT in the treatment of acute ischemic stroke at Kingston General Hospital

Rationale

The use of intravenous (IV) rt-PA, when administered within four and a half hours of onset of an acute ischemic stroke, has been shown to reduce morbidity and improve functional outcome. Evidence indicates that **time is brain** - administration of tPA as early as possible post stroke is associated with better outcomes and a smaller number needed to treat.

In select cases, during a pilot study, use of Endovascular Therapy with mechanical thrombectomy (EVT) with or without IV rt-PA may be utilized for patients with an acute ischemic stroke. The procedure consists of arterial catheterization and mechanical clot retrieval or thrombectomy, using stent retrieving devices.

5 landmark trials have demonstrated strong evidence for improved functional outcomes & reduced mortality with EVT (with or without IV rt-PA) compared to standard of care with IV rt-PA alone. Benefits of EVT were significantly greater in patients with small infarct core with proximal large arterial occlusion in the anterior circulation, and moderate-to-good collateral circulation. As a result of the impact of these trials, the Canadian Stroke Best Practice Guidelines were revised in 2015 to recommend EVT for eligible patients who meet select criteria.

The pilot at KGH will begin May 2nd, 2016 during week days only (Mon-Fri; 0800-1600h). Pending the completion of 10 cases based on select criteria, further changes including beyond week day hours will be based on the pilot findings.

In certain circumstances, rt-PA by IA route may continue to be utilized for large vessel occlusion in the posterior territory (e.g., basilar artery).

Who to decide use of rt-PA +/-EVT for the treatment of ischemic stroke?

The decision to administer rt-PA is made by the treating Neurologist. The decision for EVT with or without rt-PA is made jointly between the treating Neurologist and the Interventional Radiologist.

When a potential candidate for treatment with rt-PA +/-EVT is identified in the Emergency Department, the Charge Nurse **must** contact the KGH Switchboard to activate the "Stroke Team".

The physician who prescribes rt-PA must provide a **written order** to staff.

Essential investigations prior to the use of IV rt-PA (+/-EVT)

1. Blood work-use tubes in ASP package (**Not Mandatory to wait for all results to make decision for IV rt-PA +/-EVT; decision at discretion of treating Neurologist**)
 - a. Routine hematology (include platelets)
 - b. PT, PTT, INR
 - c. Electrolytes, BUN, creatinine, glucose, troponin
 - d. β HCG (pregnancy test) if indicated
 - e. Type and Hold 2 units
2. CT head without contrast +/- CT Angiography (CTA). For patients who could be eligible for EVT, multiphase CTA is required.

Table 1: Inclusion and Exclusion Criteria for IV rt-PA

| Inclusion criteria | Cautionary inclusion | Exclusion criteria |
|--|---|---|
| <ol style="list-style-type: none"> 1. Diagnosis of ischemic stroke causing measurable neurological deficit. 2. Deficit severity that, should it persist, would lead to a significant compromise of the patient's quality of life 3. Time of the onset must be reliably known, either from the patient, or a credible witness. 4. Duration of the stroke from the time of onset, to the beginning of administration of IV rt-PA, must be less than 4.5 hours (including the time required to complete all essential investigations). 5. If receiving heparin in the previous 48 hours, aPTT must be in the normal range. 6. Informed verbal consent obtained from the patient, or substitute decision maker. | <ol style="list-style-type: none"> 1. Myocardial infarction in previous three months. 2. Seizure at onset of stroke (this relative contra-indication is intended to prevent treatment of patients with a post-ictal deficit, or with seizure due to some other CNS lesion that precludes thrombolytic therapy. If rapid diagnosis of vascular occlusion can be made, treatment may be considered). 3. History of intracranial hemorrhage. 4. Age less than 18 years (pediatric consultation recommended). 5. Major deficit (NIHSS score greater than 22). 6. CT shows hypodensity greater than 1/3 of the hemisphere. 7. Blood glucose less than 2.7 mmol/L or greater than 22.2 mmol/L. 8. Pregnancy 9. Direct Oral Anticoagulants (DOACs) (e.g., dabigatran, rivaroxaban, apixaban) taken greater than 24 hours ago. | <ol style="list-style-type: none"> 1. Major surgery during previous 14 days. 2. History suggestive of subarachnoid hemorrhage or aortic dissection. 3. Gastrointestinal or urinary tract hemorrhage in the past 21 days. 4. Evidence of active bleeding or acute trauma (fracture) on examination. 5. Puncture of a non-compressible artery or biopsy site within 7 days, including lumbar puncture. 6. Significant head trauma or stroke in the past 90 days. 7. Blood pressure systolic greater than 180 mmHg, and/or diastolic greater than 105 mmHg at the time of rt-PA administration (see Appendix A: Management of Hypertension). 8. Serious co-morbidity, (e.g. advanced cancer, renal failure, hepatic failure) that would increase bleeding risk or limit effectiveness of outcome. 9. Coma 10. INR greater than 1.7 or platelet count less than 100,000. 11. DOACs (e.g., dabigatran, rivaroxaban, apixaban) taken within 24 hours. 12. Rapidly resolving neurologic signs. 13. Hemorrhage seen on CT head scan. 14. CNS vascular malformation, abscess or tumor. |

Table 2: Inclusion & Exclusion Criteria for EVT -Based on ESCAPE Trial Selection Criteria

Specific Inclusion Criteria for EVT:

- If IV rt-PA is given in conjunction with EVT, refer to Table 1 (inclusion/exclusion criteria for tPA). Some exceptions will apply for EVT as noted with the following criteria:
- Age 18 years or greater
- NIH Stroke Scale (NIHSS) greater than 5
- Pre-stroke functioning independently in activities of daily living in their community
- Imaging based on **all** 3 of the following:
 - Non Contrast CT with ASPECTS score of 6 or higher (small infarct core); &
 - CTA (arterial phase from aortic arch to vertex of the head) with intracranial large proximal artery occlusion in anterior circulation; &
 - Multiphase CTA with moderate to good circulation defined as 50% or more filling of the MCA pial arterial circulation
- Time to treatment based on the following:
 - Time from first slice of non-contrast CT to revascularization should be 90 minutes or less.
 - Time from the first slice of non-contrast CT to groin puncture should be 60 minutes or less.
 - Should be within 6 hours from stroke symptom onset to time of initiation of procedure (groin puncture).

Specific Exclusion Criteria for EVT:

- Intracranial bleed
- Suspected intracranial arterial dissection as a cause of stroke
- Femoral pulses absent or very difficult EVT access resulting in CT-to-recanalization time longer than 90 minutes or will result in inability to deliver EVT
- Severe contrast allergy or absolute contraindication to Iodinated Contrast
- Severe or fatal comorbid illness
- Fibromuscular Dysplasia

Care of the Patient during Treatment with rt-PA+/-EVT (see Table 3 for care if patient candidate for EVT)

1. Patients should have two IV sites, one for rt-PA and the second for other medications and in reserve.
2. Draw blood work (see pg. 1) if not done before CT.
3. No medication to be co-administered with rt-PA through IV lines.
4. Administration Guidelines:
 - a. rt-PA is administered **IV** at a dose of **0.9 mg/kg** (maximum dose of 90 mg) using rt-PA 1 mg/mL injection
 - b. **10%** of total dose is given as IV push over one minute and the remainder as an IV infusion by pump **over one hour**
 - c. Hang 50 mL normal saline when rt-PA infusion has been completed, to ensure IV line is flushed of all rt-PA
5. Vitals (BP, HR, RR) and neurological assessment [Canadian Neurological Scale (CNS)] q 15 min during drug administration. (If EVT: NIHSS or CNS to be done post EVT)
6. If an automated cuff is used, it should be loosened between readings, and position changed q 2 hours.
7. Continuous cardiac monitoring and SpO₂ monitoring.
8. ECG post initiation of IV rt-PA infusion. If patient for EVT and IVR room is ready, ECG to be done post EVT.
9. If sudden deterioration in neurological function should occur (i.e., ↓ LOC, ↑ weakness & asphasia), stop infusion and notify physician.
10. Observe tongue and oropharynx at 30 min, 45 min, 60 min and 75 min after onset of rt-PA infusion. If facial, tongue and/or pharyngeal angioedema, stop infusion and notify physician (See Appendix C for management guidelines).

Table 3: Additional Specific Care of the Patient for EVT

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| <p><u>Prep:</u></p> <ol style="list-style-type: none">1. Patient in hospital gown, no underwear2. Insert foley catheter prior to IV rt-PA (if received notification that patient is potential candidate for EVT)3. 2 Working IVs4. Shave prep both groins only if absolutely necessary-don't delay procedure for shave prep |
| <p><u>Care during procedure:</u></p> <ol style="list-style-type: none">1. Follow standard IVR care processes2. IVs infusing (consider 1 IV N/S at least 125cc/hr)3. Continuous cardiac monitoring4. Continuous BP monitoring Target SBP above 150 mmHg during the procedure until reperfusion achieved5. Avoid intubation & general anesthesia if possible. Conscious procedural sedation as per Procedural Sedation Policy & Procedural Sedation/Analgesia Order set may be all that is required. Continuous SpO₂ monitoring & titrate O₂ as per Oxygen Therapy Protocol6. If IV rt-PA administered(see above)-continue to observe for bleeding & angioedema |

Care of the Patient for the first 24 hours Following rt-PA +/- EVT (see Table 4 below for additional post EVT care)

1. If patient receives IV rt-PA alone, transfer to D4-ICU as soon as possible. If patient receives EVT, transfer to K2-ICU as soon as possible.
2. Vitals and neurological assessment (Canadian Neurological Scale (CNS)) q 1 h or more frequently as ordered (e.g. q 15 min x 2 hours, q 60 minutes x 22 hours). Notify physician if CNS >1 or change in neurological status.
3. Continuous cardiac monitoring and O₂ sat monitoring.
4. Monitor for bleeding (see Appendix B).
 - Internal bleeding (GI, GU), oozing IV sites, oral bleeding, skin
5. Monitor for angioedema (See Appendix C).
6. Bed rest-No TEDs.
7. IV 0.9 NaCl @ 75 cc/hr or as directed by physician.
8. NPO including no oral medications until swallowing ability has been determined.
9. Report BP > 180 mmHg systolic, or > 105 mmHg diastolic (See Appendix A for suggested management). Report SBP <110mmHg or < 60 mmHg diastolic.
10. Report temperature > 37.5°C.
11. Acetaminophen 650 mg PO/PR q4 h prn for temperature > 37.5°C or pain.
12. Report RR > 24/minute, or SpO₂ less than 88%.
13. If sudden deterioration in neurological function or evidence of systemic hemorrhage, consider:
 - Stat CT scan
 - Stat CBC, PTT, PT, INR, fibrinogen
 - Cryoprecipitate
14. Monitor for seizures such as: a decrease in level of consciousness, focal motor activity, prolonged uncoordinated not sustained thrashing of limbs, side to side head movements, or extensor posturing.
15. Blood glucose by glucose meter q4 h for 24h, then qid for 2 days, then reassess.
16. Notify physician for blood glucose less than 5 mmol/L or greater than or equal to 10 mmol/L.
17. CBC, electrolytes, urea, creatinine, glucose, ALT, INR, PTT, total cholesterol, HDL/LDL ratio, triglycerides fasting in morning, HbA1c.
18. Hold patient's medications as previously prescribed since patient is NPO for 24 hours.
19. No antiplatelet agents (ASA, clopidogrel, ticlopidine, aggrenox, dipyridamole) for 24 hours & until 1 brain image shows no evidence of hemorrhage. No anticoagulant agents (e.g., warfarin, enoxaparin, dalteparin, heparin, & DOACs (e.g., dabigatran, rivaroxaban, apixaban) for at least 24 hours & until 1 brain image shows no evidence of hemorrhage.
20. No arterial punctures, intramuscular injections or invasive procedures for 24 hours.
21. If arterial sheath in place, remove in accordance with physician orders (see below).
22. Repeat CT at 24 hours following rt-PA or if sudden deterioration in neurological status.

Table 4: Care of the patient for first 24 hours post EVT

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|---|
| <p><u>Pre Femoral Sheath Removal:</u></p> <ol style="list-style-type: none">1. Check ACT & remove sheath per IVR Femoral Arterial Sheath Removal Nursing Policy & Procedure & Arterial Sheath Removal Order Set |
| <p><u>Post Sheath Removal:</u></p> <ol style="list-style-type: none">1. Follow IVR Femoral Arterial Sheath Removal Policy/Procedure & Arterial Sheath Removal Order Set2. Apply bandage to puncture site3. Monitor sheath site for bleeding or hematoma, HR, BP, distal pulses and limb viability q 15 min for 1 hour then q 30 min for 3 hours then q 60 min for 20 hours, then q shift until discharge.4. Bedrest-roll q 1-2 h & keep affected limb (sheath site) straight for ordered time frame. Keep HOB no more than 30° for 6 hours post sheath removal5. Follow Care of the Patient for the first 24 hours Following rt-PA +/- EVT (above) |
| <p><u>Post EVT if Femoral Sheath Remains in Situ:</u></p> <ol style="list-style-type: none">1. Sheath to arterial line.2. Bedrest-roll q 1-2 h. Keep affected limb (sheath site) straight. Elevate HOB at 30°.3. Monitor sheath site for bleeding or hematoma, HR, BP, distal pulses and limb viability q 15 min for 1 hour then q 30 min while sheath in situ4. Consider peripheral IV N/S 75-125 cc/hr overnight |
| <p><u>During Manual Compression of Arterial Site (if Angio-Seal is not used):</u></p> <ol style="list-style-type: none">1. IVR nurse to remove femoral sheath wherever the patient is located (e.g., K2 ICU)2. Follow Femoral Sheath Removal Policy & Procedure and Arterial Sheath Removal Order Set which includes:<ol style="list-style-type: none">a. Normal saline 250 cc fluid bolus if orderedb. Monitor blood pressure q 5 minc. Monitor HR continuouslyd. Monitor sheath site and vascular status of affected limb (colour, pulses, temp) q 5-10 min |
| <p><u>General:</u></p> <ol style="list-style-type: none">1. All patients post EVT are to be transferred to K2ICU as soon as possible for at least 24 hours2. Repeat CT at 24 hours or if sudden deterioration in neurological status3. Follow the Care of the Patient for the first 24 hour following rt-PA +/- EVT (above) |

During the first 24 hours the patient should transition to Acute Stroke Collaborative Care Plan

- Appendix A: Management of Arterial Hypertension for Patients Undergoing Thrombolytic Therapy for Acute Cerebral Ischemia.
- Appendix B: Management of Hemorrhagic Complications with Use of rt-PA for Ischemic Stroke.
- Appendix C: Management of Angioedema with Use of rt-PA for Ischemic Stroke.
- Appendix D: rt-PA 1 mg/ml Infusion for Acute Ischemic Stroke Dosing Chart.

*tPA Protocol approved by Pharmacy & Therapeutics April 2001
Protocol last updated: November 28, 2016*

Appendix A

Management of Arterial Hypertension for Patients Undergoing Thrombolytic Therapy for Acute Cerebral Ischemia

Rationale:

The acute hypertensive response commonly seen in ischemic stroke does not normally require emergent treatment, because the higher pressure may actually be beneficial, and a rapid fall in pressure may extend the infarct volume. However, for patients receiving thrombolysis, very high pressures (180-230 systolic or 105-125 mm Hg diastolic) are associated with increased risk of hemorrhagic complication and justify careful antihypertensive therapy prior to receiving thrombolytic, and for 24 hours afterwards.

Recommended Treatment:

If the systolic blood pressure is 180 mmHg or greater and/or the diastolic is 105 mmHg or greater:

- Give labetalol 10 mg IV over 2 minutes
- Repeat labetalol 10-20 mg IV every 10-20 minutes PRN (to a total dose of 150 mg) to aim for BP less than 180 mmHg systolic and/or 105 mmHg diastolic.

OR

- Give hydralazine 5-20 mg IV every 20-30 minutes PRN (to a maximum of 300 to 400 mg in 24 hours) to aim for BP less than 180 mmHg systolic and/or 105 mmHg diastolic.

- Monitor BP q 15 min or more frequently during initial management. * Report hypotension (systolic BP less than 110 mmHg or diastolic BP less than 60)
- * BP monitoring must be frequent in order to detect dramatic changes in pressure. The risk of bleeding secondary to an arterial puncture must be weighed against the difficulties in monitoring rapid changes in pressure.

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Appendix B

Management of Hemorrhagic Complications with Use of rt-PA for Ischemic Stroke

The use of rt-PA carries the risk of hemorrhagic complications either intracranial or systemic.

1. Intracranial Hemorrhage:

- Clear neurologic deterioration during or within 24 hours of rt-PA infusion should be assumed to be due to intracranial hemorrhage.
- If deterioration occurs during rt-PA infusion. Stop infusion.
- Emergent CT scan
- Consider urgent neurosurgical consultation
- Consider cryoprecipitate

2. Systemic Hemorrhage:

- The management of systemic hemorrhage will depend upon the location and size of the hemorrhage, and the likelihood the bleeding can be controlled mechanically.
- If systemic bleeding is identified or suspected, stat CBC, INR, PTT, fibrinogen
- If transfusion is considered cross-match and type for 4 units packed red cells, 15-20 units of cryoprecipitate and 1 unit of single donor platelets.
- If further bleeding occurs, consider repeat of cryoprecipitate
- Monitor vital signs q 15 min
- Consider neuro-imaging studies
- Consider surgical consultation.
- Active bleeding around intravenous and arterial puncture sites may be controlled by direct pressure

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SAMPLE

Appendix C

Management of Angioedema with Use of rt-PA for Ischemic Stroke

Angioedema has been reported in 1.3% (8 of 596; 95% CI 0.6-2.6%) of patients treated with IV rt-PA therapy for acute stroke. It has been associated with previous angiotensin converting enzyme (ACE) inhibitor therapy and with a past history of angioedema reactions. The reaction has been observed approximately 45-90 minutes after the rt-PA infusion was started. Patients reported dysphagia and inspection of the tongue revealed hemilingular (ipsilateral to the side of the hemiplegia) tongue swelling. Progression to the entire tongue and oropharynx may occur.

Risk Assessment

- Inquire if patient has ever experienced angioedema in past.
- Take **ACE inhibitor** history. The following is a list of currently marketed ACE inhibitors to facilitate in their identification:

| | |
|---|--------------------------------------|
| Benazepril (Lotensin [®]) | Lisinopril (Zestril [®]) |
| Captopril (Capoten [®] , generic brands) | Perindopril (Coversyl [®]) |
| Cilazapril (Inhibace [®]) | Quinapril (Accupril [®]) |
| Enalapril (Vasotec [®]) | Ramipril (Altace [®]) |
| Fosinopril (Monopril [®]) | Trandolapril (Mavik [®]) |

- Although **angiotensin II (ATII) receptor antagonists** have not been implicated in the angioedema reaction, caution is advised in patients reporting a history of ATII antagonist use. Currently marketed ATII antagonists include:

| | |
|-------------------------------------|--------------------------------------|
| Candesartan (Atacand [™]) | Epoprosartan (Teveten [™]) |
| Irbesartan (Avapro [™]) | Telmisartan (Micardis [™]) |
| Valsartan (Diovan [™]) | Losartan (Cozaar [™]) |

- Note: Combination diuretic and ACE inhibitor or ATII formulations are also currently marketed and should be noted.

Monitoring Parameters

- Observe for facial, tongue, and/or pharyngeal angioedema 30 minutes, 45 minutes, 60 minutes and 75 minutes after initiation of IV rt-PA infusion and periodically for 24 hours afterwards
- Continuous O₂ monitoring during rt-PA IV infusion and for 24 hours afterward

Management

Treat angioedema aggressively with the following agents until resolution:

- Diphenhydramine (Benadryl) 50 mg IV Q4H
- Ranitidine 50 mg IV Q8H
- If severe, consider Hydrocortisone 100 mg IV or Methylprednisolone 80 mg IV Q8H
- Avoid use of epinephrine due to possibility of increasing risk of intracerebral hemorrhage secondary to sudden rise in blood pressure

Approved by Pharmacy and Therapeutics April 2001

Reference: Hill M et al. Anaphylactoid reactions and angioedema during alteplase treatment of acute ischemic stroke. *CMAJ* 2000; 162(9):1281-4.

Appendix D

rt-PA 1 mg/ml Infusion for Acute Ischemic Stroke

| Patient weight (kg) | 10% bolus (mL) | Infusion Dose Over One Hour Where 1mg = 1cc | Total t-PA dose: 0.9 mg/kg |
|---------------------|----------------|---|----------------------------|
| 50 | 5 | 40 | 45 |
| 51 | 5 | 41 | 46 |
| 52 | 5 | 42 | 47 |
| 53 | 5 | 43 | 48 |
| 54 | 5 | 44 | 49 |
| 55 | 5 | 45 | 50 |
| 56 | 5 | 45 | 50 |
| 57 | 5 | 46 | 51 |
| 58 | 5 | 47 | 52 |
| 59 | 5 | 48 | 53 |
| 60 | 5 | 49 | 54 |
| 61 | 6 | 49 | 55 |
| 62 | 6 | 50 | 56 |
| 63 | 6 | 51 | 57 |
| 64 | 6 | 52 | 58 |
| 65 | 6 | 53 | 59 |
| 66 | 6 | 53 | 59 |
| 67 | 6 | 54 | 60 |
| 68 | 6 | 55 | 61 |
| 69 | 6 | 56 | 62 |
| 70 | 6 | 57 | 63 |
| 71 | 6 | 58 | 64 |
| 72 | 7 | 58 | 65 |
| 73 | 7 | 59 | 66 |
| 74 | 7 | 60 | 67 |
| 75 | 7 | 61 | 68 |
| 76 | 7 | 62 | 68 |
| 77 | 7 | 62 | 69 |
| 78 | 7 | 63 | 70 |
| 79 | 7 | 64 | 71 |
| 80 | 7 | 65 | 72 |
| 81 | 7 | 66 | 73 |
| 82 | 7 | 66 | 74 |
| 83 | 8 | 67 | 75 |
| 84 | 8 | 68 | 76 |
| 85 | 8 | 69 | 77 |
| 86 | 8 | 70 | 77 |
| 87 | 8 | 70 | 78 |
| 88 | 8 | 71 | 79 |
| 89 | 8 | 72 | 80 |
| 90 | 8 | 73 | 81 |
| 91 | 8 | 74 | 82 |
| 92 | 8 | 75 | 83 |
| 93 | 8 | 75 | 84 |
| 94 | 9 | 76 | 85 |
| 95 | 9 | 77 | 86 |
| 96 | 9 | 78 | 86 |
| 97 | 9 | 79 | 87 |
| 98 | 9 | 79 | 88 |
| 99 | 9 | 80 | 89 |
| 100 + | 9 | 81 | 90 |

Instructions: Administer 10% bolus dose IV over one minute and the remainder as an IV infusion over one hour. The maximum dose is 90 mg.