

**Optimal Post Tpa-Iv Monitoring in Ischemic Stroke
(OPTIMIST)**

NCT02039375

November 18, 2013

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1. Abstract

Intravenous (IV) tissue plasminogen activator (tPA) is the only FDA-approved therapy for treatment of acute ischemic stroke. In the United States, IV tPA is typically administered in the Emergency Department (ED) for patients presenting with acute ischemic stroke within 4.5 hours of symptom onset. It is current practice that post-tPA patients are monitored in an intensive care unit or intensive care unit (ICU)-like setting for at least 24 hours, in part due to frequent vital sign and neurological monitoring that is currently the standard of care. However, rigorous evidence to support this practice is largely lacking. In a retrospective analysis of 153 patients receiving IV tPA at Johns Hopkins Hospital (JHH) and Johns Hopkins Bayview Medical Center (JHBMC), we have shown that most patients who have ICU needs in the first 24 hours after tPA administration develop such needs by the end of the tPA infusion. Patients without ICU needs by the end of the tPA infusion in the ED do not require further ICU resources if their presenting NIH Stroke Scale (NIHSS) is below 10. Therefore, we seek approval to perform a prospective clinical trial that aims at establishing the first proof-of-concept and feasibility of whether tPA for acute ischemic stroke can safely be administered and subsequently monitored in a non-ICU setting for a select subpopulation of stroke patients with low NIHSS ($\text{NIHSS} \leq 9$) who are without ICU needs by the end of the tPA infusion. Identifying post-tPA patients who can be safely monitored in a non-ICU environment may improve cost-effective utilization of ICU resources and reduce the length of hospitalization for stroke patients.

2. Objectives

1. To establish that post-tPA monitoring for patients with minor stroke symptoms ($\text{NIHSS} \leq 9$) can be done safely in a non-ICU setting.
2. To establish that the functional outcome of post-tPA patients monitored in a non-ICU setting is no worse than for patients who were monitored in the ICU.

3. Background

Stroke is a leading cause of disability in adults in the US. Currently, IV tPA is the only FDA-approved acute therapy for treatment of ischemic stroke, and is routinely administered to patients in the ED within 4.5 hours of onset of stroke symptoms. After tPA administration in the ED, the patients are routinely monitored in the neurocritical care unit (NCCU) for at least 24 hours for frequent neurological exams and vital sign checks before being eligible to be transferred to a floor bed. While this practice is the current standard of care, there is no rigorous scientific evidence to suggest that all patients require intensive monitoring in the NCCU. In addition, ICU care is costly and ICU resources are scarce. We have recently analyzed the critical care needs and interventions of 153 patients who received IV tPA for acute ischemic stroke at JHH and JHBMC between 2010 and 2013. We found that over 80% of post-tPA patients did not have critical care needs (Faigle et al,

manuscript submitted). Furthermore, our data show that 93% of patients without critical care needs by the end of the tPA infusion continue to have an uneventful hospital course with no further critical care needs. The risk of critical care needs for patients presenting with minor stroke symptoms, defined as a presenting NIHSS of 9 or less, was less than 1% if no ICU indication was present by the end of the tPA infusion. We hypothesize that patients who receive IV tPA for acute ischemic stroke in the ED may be safely monitored in a non-ICU environment if they do not have an ICU indication by the end of the tPA infusion and if their presenting NIHSS is below 10.

4. Study Procedures

Design:

The study is a multi-center (2 clinical sites) single arm, open label, pilot clinical trial. The aim is to provide proof-of-concept testing for the safety of non-ICU care in post-tPA patients in acute stroke. The null hypothesis (Ho) is that patients who are monitored in a non-ICU environment post-tPA administration will have ICU needs exceeding 6% of all patients. Six percent was chosen as a cut-off because this is the expected rate of hemorrhage after tPA administration in all stroke patients based on published literature.

The alternative hypothesis (Ha) is that no more than 6% of patients who are monitored in a non-ICU environment post-tPA administration will develop ICU needs.

Treatment Regimen:

IV tPA 0.9mg/kg, maximum of 90mg. Administered by the standard protocol: 10% of the dose by Intravenous bolus injection, followed by infusion of the remainder over 1 hour.

Patients presenting to JHH or JHBMC with signs and symptoms of acute ischemic stroke will undergo evaluation for eligibility of IV tPA in the ED according to the current standard of care: Treatment with IV tPA will be initiated for patients with presumed ischemic stroke presenting within 4.5 hours of symptom onset with a preferred target door to needle time of 60 minutes or less from arrival to the ED. As part of the routine care prior to IV tPA administration all patients will have received the following procedures/tests:

1. History, physical examination, and neurological examination including NIHSS.
2. EKG, CBC, electrolytes, creatinine and BUN, PT and PTT.
3. Two intravenous catheters will be started.
4. A non-contrast CT scan of the brain or MRI of the brain per the standard of care protocol at the clinical site.

Patients will receive routine care during the hour of tPA infusion in the ED according to the current standard of care.

Study Interventions:

Patients ages 18-80 are eligible to be enrolled in the study if they present with an NIHSS <10 and if they do not have ICU needs by the end of the tPA infusion. A repeat NIHSS is recorded at the end of the tPA infusion by a member of the stroke team, and the patient or patient representative is approached for enrollment in the study if repeat NIHSS <10 at the end of the tPA infusion.

Once the patient has agreed to participate and has signed the consent form, a subject ID number will be assigned. The subject will then be monitored per the non-ICU care protocol (Hopkins protocol) with neurological exams and vital sign checks as specified below. Prior to transfer to the Brain Rescue Unit (BRU) (at JHH site) or Intermediate Medical Care (IMC) (at JHBMC site), subjects will undergo neurological exams and vital sign checks in the ED every 15 minutes during the first hour after tPA completion according to the current standard of care.

Patients will then be moved to the BRU (at JHH) or IMC (at JHBMC) by the end of the first hour after the end of infusion. In order to facilitate bed availability for subjects enrolled in this study, a bed will be made available in an expedited fashion as soon as the decision to administer tPA in a potential subject is made (patients with presumed acute ischemic stroke presenting with NIHSS <10). The admitting neurology resident accompanies the patient to the BRU (at JHH) or IMC (at JHBMC) and gives verbal sign-out to the receiving nurse at the bedside, as it is current standard of

care. Sign-out to the receiving physician (senior resident on the stroke inpatient service at JHH or covering chief resident at JHBMC) will be given at the bedside upon arrival.

The non-ICU protocol (Hopkins protocol) consists of the following schedule for neurological exams and vital sign checks by a stroke-trained nurse: at the time of admission to the unit, then again 1 hour after admission, then every 2 hours for another 8 hours, and then every 4 hours until 24 hours post-tPA are complete. This schedule is slightly more intense monitoring than the current standard of care for non-tPA acute stroke admissions, however, is less intense than NCCU monitoring for post tPA patients.

Subjects will be under the care of the admitting physician that may also be the study investigator. During the first 24 hours all patients will receive a formal NIHSS evaluation for any worsening in neurological exam as determined by the subject's nurse. The NIHSS will be performed by the neurology resident or member of the inpatient team. Nurses will have special training in caring for post tPA patients, and will be familiar with risks and warning signs of tPA related hemorrhage and other complications.

To ensure safety of subjects monitored per non-ICU protocol at JHH, a rapid response (RRT) will be activated if the subject develops any new indication for ICU admission. An RRT includes a prompt evaluation by the on-call NCCU fellow with potential transfer to the NCCU if deemed clinically appropriate. RRT activation for subjects at JHBMC includes discussion with the neurology Chief resident and NCCU fellow for potential transfer to the NCCU if deemed indicated.

Criteria for RRT activation for potential ICU transfer are at the discretion of the treating medical team. In addition to commonly accepted criteria for ICU transfer, worsening of the neurological exam of >3 points on the NIHSS will trigger a STAT head CT and transfer to ICU for intense monitoring if the CT reveals intracerebral hemorrhage or increasing cerebral edema with signs of mass effect. This is based on previously established criteria in the ECASS trial, in which neurologic worsening with an NIHSS >3 was used to evaluate for potential symptomatic intracranial hemorrhage¹.

Other commonly accepted criteria for need for ICU transfer may include, but may not be limited to, the following:

- uncontrolled hypertension requiring active titration of IV antihypertensives (more than two doses within 30 minutes or frequent dosing (e.g., q 1hr x 3 doses))
- need for vasopressors either for symptomatic systemic hypotension or blood pressure augmentation
- need for invasive hemodynamic monitoring
- uncontrolled hyperglycemia requiring IV Insulin
- respiratory compromise resulting in either initiation of bilevel positive airway pressure (BiPAP) or mechanical ventilation
- arterial bleeding
- management of cerebral edema and increased ICP
- need for neurosurgical intervention such as decompressive craniectomy
- interventional angiography with or without intervention

Once the decision is made to move the patient to the NCCU, subjects will receive routine NCCU care and the subject will be adjudicated as meeting the primary outcome.

After 24 hours (+/- 4 hours) patients will receive either a head CT without contrast or an MRI brain as it is the current standard of care, and will receive an NIHSS by a member of the study team.

Thereafter, patients will continue to receive standard care for stroke patients, and will be discharged from the hospital, when medically stable, to the appropriate rehabilitation setting, if any. At the time of discharge all patients will receive a modified Rankin score, and NIHSS.

All patients will return for a follow-up visit at 90 days and will receive a modified Rankin score, and NIHSS. This will be the secondary outcome.

The subject's involvement with this study will end at 90 days after the assessment.

5. Inclusion/Exclusion Criteria

Subject selection:

Both sites for this study are certified stroke centers (JHH and JHBMC). Patients presenting to the ED will be identified upon arrival as acute stroke patients and screened by the ED personnel for time of onset (this is standard procedure). The stroke team will evaluate the patients with a history and neurological exam as well as EKG, laboratory studies and a non-contrast head CT or MRI per the standard of care at the clinical site. Patients with presumed acute ischemic stroke will receive IV tPA in the usual fashion per the current standard of care if presenting to the ED within 4.5 hours of symptoms onset. Every patient receiving IV tPA for presumed acute ischemic stroke will be screened for the presence of inclusion criteria and absence of exclusion criteria, and if found to qualify for the study will be asked to participate after reviewing the details of the study and consent form.

The investigator will explain the clinical trial to the patient or the Legally Authorized Representative (LAR) and will review the consent form, answering any questions. This will be conducted in a private and calm setting as much as it is possible in the ED. The patient or LAR will be given the consent form to review and a copy of signed consent form as well.

Subjects will receive a subject ID that will be a sequential numerical code.

Inclusion criteria:

Subjects will be eligible if the following criteria are met:

- Ability to provide written informed consent (or a LAR available to provide informed consent) and comply with study assessments for the full duration of the study.
- Age 18-80 years

Patient-related considerations (All criteria need to be met):

- Patients to be included will be diagnosed as having an acute ischemic stroke by history and physical exam and receive IV tPA within 4.5 hours of symptom onset according to current guidelines for acute stroke care.
- NIHSS at presentation <10
- Patients do not have ICU needs in the judgment of the treating ED physician or neurologist by the end of the tPA infusion
- NIHSS at the end of tPA infusion <10

Other considerations:

- Some patients will not be able to provide informed consent. In these cases consent will be obtained from the Legally Authorized Representative (LAR).
- Patients that in the judgment of the investigator will not be able to comply with the follow up examinations due to known non-compliance, residence is distant, terminal illness, etc; will not be candidates for inclusion in the trial.

Exclusion criteria:

For patients receiving IV tPA according to the current standard of care, the following exclusion criteria apply:

- Age <17 or >80
- ICU need or indication by the end of the tPA infusion
- NIHSS >9 at presentation or at the end of the tPA infusion
- Indication/need for endovascular recanalization therapy

6. Drugs/ Substances/ Devices

No experimental drug will be used in this trial. All patients will receive IV tPA per the standard of care. Tissue plasminogen activator (tPA) is FDA-approved for treatment of acute ischemic stroke, and will be administered at the standard dose for treatment of acute stroke: 0.9mg/kg, 10% IV bolus, and the rest by IV continuous infusion over one hour. Maximum dose is 90mg. tPA Indication and mode of IV tPA administration will occur according to the current standard of care.

7. Study Statistics

Baseline Demographics:

The sample size will be 50 patients, to assess the safety of non-ICU monitoring in post-tPA patients selected according to above criteria. The number of patients receiving IV tPA for acute ischemic stroke at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center is approximately 75 per year, fairly evenly divided between the 2 locations. Based on our retrospective analysis of 153 patients over 3 years between 2010 and 2012, 85 of 153 patients would have been eligible to participate in this study based on above inclusion and exclusion criteria. Assuming a constant rate of tPA administration per year, this would yield about 27 study subjects per year at JHH and JHBMC, assuming a rate of agreement of 65%. Based on this assessment, this study can be completed in less than two years.

Safety analysis:

Because this study is designed to assess safety, the safety analysis is the same as the primary outcome analysis, which is the assessment of the rate of ICU needs and need for ICU transfer developing in the first 24 hours after IV tPA administration. A DSMB (composed of one member independent of the investigator team) will conduct an analysis of the rate of ICU transfer in the study subjects.

Need for ICU transfer (events) for patients monitored in the non-ICU setting will be evaluated after each subject completes 24 hours of post-tPA monitoring. During the phase of the study in which there are 1-9 subjects, the study will stop at any point there are two events in this group. During the phase of the study in which there are 10-20 subjects, the study will stop at any point if there are three events. During the phase of the study in which there are 20-40 subjects, the study will stop at any point if there are four events. During the phase of the study in which there are 40-50 subjects, the study will stop at any point if there are five events.

Primary endpoint:

- Need for ICU care/interventions (including intracerebral hemorrhage or cerebral edema with mass effect) within the first 24 hours after IV tPA administration will be the primary outcome measure.

Secondary endpoints:

- NIHSS at 24 hours
- NIHSS at discharge
- Modified Rankin Scale at discharge
- NIHSS at 90 days
- Modified Rankin Scale at 90 days
- Mortality at 90 days

Analysis for the secondary endpoints will be done comparing outcomes of study subjects with matched (age, race, NIHSS) controls from our de-identified stroke database of patients receiving IV tPA for acute ischemic stroke under the standard protocol.

Subject discontinuation:

Subjects have a right to withdraw from the study at any time. Subjects that decide to withdraw from the study within the first 24 hours will receive standard of care at the time of withdrawal. No data will be collected on the patient after voluntary withdrawal from the study.

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening condition. The IRB, NINDS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected, may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

8. Risks

Risks potentially associated with non-ICU monitoring may result from delayed recognition of medical or neurological deterioration, with limited capability of rapid intervention in a non-ICU setting.

Most complications related to IV tPA administration are neurological deterioration secondary to intracerebral hemorrhage. In our retrospective analysis, almost all patients who developed ICU needs after IV tPA developed such needs during the tPA infusion. In the present study, subjects are being monitored in the ED with frequent neurological examinations and vital sign checks during the tPA infusion, and for up to an additional hour, as it is the current standard of care. In the non-ICU setting, a stroke trained nurse will assess the patient upon admission to the floor, and then again after 1 hour, thereby ensuring adequate frequency of examinations and vital sign checks in the most critical post-tPA period. Thereafter, neurological exams and vital sign checks will be less frequent, every 2 hours for 8 hours, and then every 4 hours until 24 hours post-tPA are complete. Nurses will have special training in caring for post tPA patients, and will be familiar with risks and warning signs of tPA related hemorrhage and other complications. Per protocol, any change in neurological exam will result in a formal evaluation by the covering neurology resident or member of the inpatient team who will obtain an NIHSS. At JHH an RRT (with evaluation by the on-call NCCU fellow) for potential transfer to the NCCU will be activated for any increase in NIHSS > 3 points from baseline (post-tPA NIHSS). Similarly, any medical deterioration requiring ICU care in the judgment of the provider will result in activation of an RRT with potential transfer to the NCCU. Similarly, at JHBMC RRT activation for subjects will follow the same criteria, and includes discussion with the neurology Chief resident and NCCU fellow for potential transfer to the NCCU if deemed indicated.

Safety assessments will consist of monitoring and reporting adverse events (AE) and serious adverse events (SAE) that are considered to be related to non-ICU monitoring, all events of death, and any study specific issue of concern.

An AE is defined as any unfavorable and unintended sign, symptom, or disease temporally associated with non-ICU monitoring.

This includes the following:

- Any event or change in condition within the first 24 hours after tPA administration that requires ICU care or ICU intervention.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with ischemic stroke that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

An AE should be classified as an SAE if:

- It results in death
- It is life threatening
- It requires prolonged hospitalization
- It results in persistent or significant disability/incapacity

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately.

9. Benefits

By potentially avoiding an unnecessary ICU stay, participants may benefit from an expedited stroke work-up and reduced length of hospital stay. Admission directly to the floor would result in less frequent interruptions for neurological exams and vital sign checks, which may improve quality of sleep. In addition, bypassing ICU care would reduce the number of hand-offs between different providers and provider teams, and thereby reduce the chance for medical errors. Avoiding unnecessary ICU admission would greatly reduce cost for stroke admissions and reduce the financial burden on society associated with acute stroke care.

10. Payment and Remuneration

There will be no payment to participants.

11. Costs

There are no anticipated additional costs to participants.

12. References

(1) Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-1329.