Thrombolysis for Acute Ischemic Stroke after Recent Myocardial Infarction

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Abstract
Intravenous tissue plasminogen activator is currently the only FDA approved medical treatment for acute ischemic stroke with current relative contraindications that include recent myocardial infarction and elevated partial thromboplastin time. We report three cases where patients having subacute myocardial infarction received intravenous thrombolysis for acute ischemic strokes. Results varied from full recovery to cardiogenic shock and death. Notable differences between the patients with good and bad outcome included the presence of transmural myocardial infarction and the onset time from myocardial infarction to administration of intravenous thrombolysis. These cases highlight that when faced with the clinical dilemma of concomitant myocardial infarction and acute ischemic stroke, intravenous thrombolysis and stroke deficit must be balanced against perceived contraindications.

Keywords — cardiac rupture, hemorrhagic transformation, myocardial infarction, stroke, tissue plasminogen activator, thrombolysis

We report a series of cases where patients presented with concomitant MI and large-vessel AIS. Given the large and neurologically devastating potential of each large vessel occlusion, each patient received IVtPA with variable results.

Our Experience #1
A 46-year-old man, with a medical history of coronary artery disease (triple coronary artery bypass grafting six years prior), hypertension, hypercholesterolemia, diabetes, and recent smoking cessation presented to an outside Emergency Department (ED) with precordial pain, nausea, and diaphoresis. His symptoms began during physical activity and persisted at rest. His troponin-I levels increased from 0.447 ng/mL to 37.90 ng/mL. Electrocardiogram (ECG) showed ST-segment elevation (STEMI) on the aVL lead with ST-depression over leads II, III and aVF (Figure 1). Unfractionated heparin infusion was started and titrated per cardiac protocols. He underwent coronary angiography without intervention due to extensive, multi-vessel atherosclerotic disease; heparin infusion was continued. Twenty-four hours after the coronary angiogram, the patient experienced sudden onset of aphasia with right facial palsy and right arm drift; National Institutes of Health Stroke Scale (NIHSS) score was 6. Heparin drip was interrupted and a stroke neurologist from a tertiary center was contacted for assistance.

Other than the recent STEMI, no other contraindications were noted. Non-contrast computed tomography (CT) of the head was unremarkable (Figure 2), and CT angiography demonstrated occlusion of the left anterior division of the middle cerebral artery (MCA) as well as 80% stenosis of the left carotid bulb from non-calcified plaque (Figure 3).

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Figure 1: Initial EKG upon presentation with chest pain showing ST segment elevation on aVL lead with ST depression over leads II, III and aVF.
Given the debilitating stroke deficit and the outside hospital's lack of neuro-endovascular capacity, decision was made for IVtPA administration. IVtPA was initiated 45 minutes after symptom onset, and the patient was transferred to the Tertiary Hospital for further evaluation and treatment.

Immediately following treatment, the patient initially improved to an NIHSS score of 5, however his NIHSS score then worsened to 17. Repeat head CT showed subtle left MCA ischemic abnormalities without bleeding (Figure 4). At this time, it was noted that the actual aPTT in the outside hospital records was 41 rather than the 24 that was erroneously reported for remote IVtPA administration. As the patient had significantly worsened even after IVtPA administration, Endovascular was consulted with resultant mechanical thrombectomy and recanalization of the L-MCA occlusion. Post-procedural NIHSS score improved to 5. The patient was transferred and monitored in the intensive care unit, but soon required vasopressor for hemodynamic instability.

Twelve hours after the thrombectomy, the patient became tachycardic to 120 beats/minutes, but remained neurologically stable. Vasopressor was continued with adequate hemodynamic control. Magnetic resonance imaging (MRI) brain demonstrated scattered small, acute embolic infarcts in the left MCA territory (Figure 5) without evidence of hemorrhage on the gradient echo sequence.

However, after the MRI, the patient soon developed bradycardia that rapidly evolved into asystole. Cardiopulmonary resuscitation was immediately performed and continued for 30 minutes without success, and the patient was declared dead.

Our Experience #2

A 72-year-old man, with a medical history of hypertension, presented to an outside ED with acute onset dysarthria, right facial droop, and right upper and lower extremity weakness and paresthesia. In addition, he reported retrosternal, non-exertional, burning-like chest discomfort described as "heaviness" with no dyspnea or palpitation. His admission NIHSS score was 7 and the decision was made to give IVtPA about 43 minutes after symptom onset.

The patient was transferred to a tertiary hospital with a post-IVtPA NIHSS score of 1. Diffusion-weighted images showed no evidence of acute ischemic changes. His troponin-I levels trended up from < 0.015 ng/mL to 5.540 ng/mL, and ECG showed ST-depression over leads II, III, aVF, V5, and V6. The patient was started on heparin drip and admitted to the intensive care unit. Two days later, he underwent a cardiac catheterization that showed triple-vessel coronary artery disease. No intervention was performed with recommendations for coronary artery bypass graft surgery. Soon after the cardiac catheterization, he complained of acute onset of binocular blindness with worsening NIHSS of 3. MRI brain showed bilateral cerebellar and bilateral posterior occipital acute ischemic changes. The patient received IVtPA again about 2 hours and 7 minutes after onset of blindness and 48 hours after onset of NSTEMI. The patient remained hemodynamically stable and had no complications besides bleeding at his femoral artery site from the prior cardiac catheterization. The patient eventually regained his vision in both eyes and had an NIHSS score of 0 upon discharge to home.
Our Experience #3

A 48-year-old woman, with a medical history of hypertension, hyperlipidemia, coronary artery disease (diffuse triple-vessel disease on cardiac catheterization three years prior), chronic obstructive pulmonary disease, and morbid obesity presented to an outside ED for acute-onset weakness and paresthesia that started on the left side of her face and then progressed to her left arm, one day prior to her admission. Her admission NIHSS was 5. The patient reported constant, non-radiating, central chest pain, nausea and emesis, and a sensation of “trapped gas”. She was transferred to a territory medical center. Troponin-I trended up from 0.198 ng/mL to 5.780 ng/mL. ECG showed non-specific T-wave flattening over V5 and V6, but no Q waves or ST segment changes. MRI brain showed no evidence of ischemic changes. The patient was started on heparin drip, beta blockers and aspirin for presumed NSTEMI. The next day, during her cardiac catheterization, she became agitated, and the cardiac catheterization was aborted.

 Shortly afterward, she had an acute change mental status change, right-side hemiplegia, and an NIHSS score 18. Labs showed an INR of 1.0 and aPTT of 26.2 seconds. IVtPA was given about an hour and forty eight minutes after onset of symptoms and 47 hours after NSTEMI. MRI brain showed acute ischemic strokes in the left MCA distribution, and magnetic resonance angiogram of head and neck showed no high-grade stenosis or occlusion. Although her hospital course was complicated by respiratory failure, methicillin-resistant Staphylococcus aureus pneumonia, and tonic-clonic seizures, she remained hemodynamically stable, and had no further cardiac complications. She received a percutaneous tracheostomy and endoscopic gastrostomy tube and was discharged to a skilled nursing facility.

DISCUSSION

As IVtPA is still the only FDA-approved medical treatment for AIS and “recent” MI is a known relative contraindication for IVtPA in certain guidelines 3, fewer options are left for patients suffering from the severely disabling and potentially life-threatening sequelae of AIS. “Recent” MI represents one specific contraindication that must be re-evaluated because of the large incidence of AIS that follow MI—one study estimating a 44-fold increase in stroke risk after MI 5 and another showing that 87% of AIS after MI occurring within the first 5 days 6. These cases highlight the need to re-evaluate what are perceived as contraindications to systemic thrombolysis in patients with AIS—in particular, recent MI and cardiac complications.

MI in the previous three months is a relative contraindication for IVtPA in AIS patients 3 with the rationale that thrombolysis predisposes to cardiac wall rupture, hemopericardium, and cardiac tamponade 7. However, as this case series demonstrates, a uniform approach to this perceived contraindication must be weighed against the deficits elicited by AIS as some patients may actually benefit with minimal complications.

The correct time frame for peak vulnerability to cardiac rupture and mechanism by which thrombolytic agents induce cardiac rupture is still uncertain. In MI, the incidence of cardiac rupture after IVtPA was 1.7% with most occurring within 48 hours of MI 8. However, indirect histopathological evidence suggested that the risk for cardiac rupture was highest within the first 7 weeks 7.
One mechanism proposed is that thrombolytic agents stimulate the breakdown of interstitial collagen in the infarcted myocardium, which increases the risk of cardiac rupture. Murine models have shown that pathological activation of matrix metalloproteinase and severe inflammatory responses via activation of macrophages may also play a role in cardiac rupture.

Becker et al. evaluated 122,243 patients who received IVtPA and found an incidence of cardiac rupture to be less than 1%. Although, histological evidence in cardiac rupture that occurred prior to the use of intravenous thrombolyis suggested that STEMI is a prerequisite for cardiac rupture, the role of transmural infarction—STEMI vs NSTEMI—as a risk factor for cardiac rupture after IVtPA is uncertain. Case reports do exist showing cardiac rupture in patients presenting with devastating AIS and subacute (2-4 days old) STEMI. Similarly, Patel et al. evaluated 102,060 patients and found isolated cardiac tamponade to only occur in 0.85% of their population with one independent predictor being STEMI location of the anterior wall.

Of our cases where patients received IVtPA for potentially devastating AIS and had subacute MI, patient 1 fared poorly and passed away from cardiogenic shock. As shown in Table 1, in relation to onset of his MI, he received IVtPA at an earlier period—1 day vs. 2 days for patients 2 and 3—and more importantly, had a STEMI. Although the lack of autopsy results prevents a definitive explanation of his cardiogenic shock, cardiac rupture (versus propagation of the coronary ischemia from holding the heparin drip) remains the most viable etiology. While interval time from the MI to IVtPA remains unclear as a contraindication, the presence of a subacute transmural infarction may be a reasonable contraindication for introducing intravenous thrombolysis. However, this “subacute” period must be better defined as guidelines put forth by the ACCF/AHA state that it is reasonable to give intravenous thrombolysis to patients presenting within 12 hours and even 24 hours of STEMI onset.

This case series suffers from a limited sample size that makes definitive conclusions difficult to ascertain. However, the potential good outcomes that may result from thrombolysis of patients with concomitant AIS and MI shows that validity of this contraindication must be further explored in prospectively collected data. Although the safety of IVtPA is improving, clinical trials continue to push the boundaries of thrombolysis with adjuvant therapies such as argatroban that amplify post-IVtPA recanalization with good safety results. IVtPA coupled with promising new data on efficacy of stent retrieval devices for AIS will likely demand revisiting perceived contraindications and perhaps early initiation of anticoagulants to maintain cerebral vessel patency similar to post-coronary intervention management. As the landscape of AIS treatment changes, further studies will have to be conducted to evaluate relative contraindications such as MI and reasonable time intervals for peak vulnerability to cardiac rupture.

### Table 1: Clinical Characteristics of patients with myocardial infarction and ischemic stroke receiving intravenous thrombolysis

<table>
<thead>
<tr>
<th>MI type</th>
<th>Time interval from MI to IVtPA</th>
<th>Time interval from AIS onset to IVtPA</th>
<th>Cardiac result</th>
<th>Stroke result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>STEMI</td>
<td>24 hrs</td>
<td>45 min</td>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Patient 2</td>
<td>NSTEMI</td>
<td>48 hrs</td>
<td>127 min</td>
<td>None</td>
</tr>
<tr>
<td>Patient 3</td>
<td>NSTEMI</td>
<td>47 hrs</td>
<td>108 min</td>
<td>None</td>
</tr>
</tbody>
</table>

### References

1. Zivin JA. Acute stroke therapy with tissue plasminogen activator (tPA) since it was approved by the U.S. Food and Drug Administration (FDA). Annals of neurology 2009;66:6-10.