Intravenous thrombolysis in acute ischemic stroke patients with negative CT perfusion: a case series

Ratnesh Mehra, Chiu Yuen To, Omar Qahwash, Boyd Richards and Richard D Fessler II

Abstract
Background: Computed tomography perfusion (CTP) is a commonly used modality of neurophysiologic imaging to aid the selection of acute ischemic stroke patients for neuroendovascular intervention by identifying the presence of penumbra versus infarcted brain tissue. However, many patients present with evidence of cerebral ischemia with normal CTP, and in that case, should intravenous thrombolytics be given?

Purpose: To demonstrate if tissue-type plasminogen activator (tPA)-eligible stroke patients without perfusion defects demonstrated on CTP would benefit from administration of intravenous thrombolytics.

Material and Methods: We retrospectively identified patients presenting with acute ischemic symptoms who received intravenous tPA (IV-tPA) from January to June 2012 without a perfusion defect on CTP. Clinical and radiographic findings including the NIHSS at presentation, 24 h, and at discharge, symptomatic and asymptomatic hemorrhagic transformation, and the modified Rankin score at 30 days were collected. A reduction of NIHSS of greater than 4 points or resolution of symptoms was considered significant.

Results: Seventeen patients were identified with a mean NIHSS of 8.2 prior to administration of intravenous thrombolytics, 3.5 after 24 h, and 2.5 at discharge. Among them, 13 patients had significant improvement of NIHSS with a mean reduction of 6.15 points at 24 h. One patient initially improved but had delayed hemorrhagic transformation and died. Two patients had improvement in NIHSS but were not significant and two patients had increased in NIHSS at 24 h, although one eventually improved at discharge. There was no asymptomatic hemorrhagic transformation. Mean mRS at 3 months is 1.76.

Conclusion: The failure to identify a perfusion deficit by CTP should not be used as a contraindication for intravenous thrombolytics. Criteria for administration of intravenous thrombolytics should still be based on time from symptom onset as previously published by NINDS.

Keywords
CT, MR diffusion/perfusion, thrombolysis, physiological studies

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Introduction
Treatment of acute ischemic stroke has evolved in recent years largely due to improved triage and systems organization to streamline evaluation of stroke patients. There has been a corresponding improvement in delivery of intravenous tissue-type plasminogen activator (IV-tPA) from 2005 to 2009, with rates increasing from 1.1% to 5.2% (1). Time of known presentation is a significant limitation relative to IV-tPA administration in many patients. In order to expand the number of patients who may be eligible for treatment, tertiary stroke centers have incorporated
neurophysiologic imaging to identify patients who may potentially benefit from endovascular therapy. Neuroendovascular therapy has a longer treatment window compared to IV-tPA (2–4). Academic debates are ongoing with regards to the best available imaging modality, i.e. non-enhanced computed tomography (NECT) with Alberta Stroke Program Early CT (ASPECT) score, computed tomography angiography (CTA), computed tomography perfusion (CTP), and magnetic resonance (MR) diffusion and MR perfusion. Due to limited availability and accessibility of MR imaging (MRI), CTP is among one of the most commonly used neurophysiologic imaging modalities to determine the presence of salvageable brain tissue. Several studies support the use of CTP to evaluate for IV-tPA candidates beyond the 4.5-h window. As a corollary, could a negative CTP be used to exclude patients from IV-tPA administration? As part of the stroke protocol at our institution, CTP is routinely obtained on patients present with symptoms of acute ischemic stroke and is rapidly interpreted. For IV-tPA eligible patients with signs and symptoms of acute ischemia without perfusion defects on CTP, should intravenous thrombolytic still be administered?

Material and Methods
We performed a retrospective review of all patients who received IV-tPA for acute ischemic stroke in our health system between January and June 2012. Included were patients who had no perfusion defects on CTP and received IV-tPA. A total of 57 patients received IV-tPA (0.9 mg/kg with a max dose of 90 mg) at our centers during this period. Seventeen patients met the inclusion criteria for the study and their clinical and radiographic characteristics are shown in Table 1. Their NIH stroke scale scores were recorded at presentation, 24 h after administration of IV-tPA, and at discharge. A reduction of 4 points on NIHSS (National Institute of Health Stroke Scale) or resolution of symptoms within 24 h was considered significant improvement consistent with the original NINDS (National Institute of Neurological Disorder and Stroke) study (5). Outcome is analyzed based on 30-day mRS (modified Rankin Scale), a score of 2 or less is considered favorable.

Results
The average age of our patients was 61.5 years. Average time from symptom onset to infusion of IV-tPA was 167.1 min (data from patient 17 was not recorded). Mean NIHSS at presentation was 8.24 (range, 3–15), 3.47 after 24 h of IV-tPA administration, and 2.5 at discharge. Thirteen patients had significant improvement in symptoms (76.4%; mean NIHSS reduction 6.15; range, 3–12) at 24 h post IV-tPA. Of the remaining four patients, two had less than significant improvement, and two had increased of NIHSS at 24 h.

| Personal identification number | Age (years) | Time of symptom onset to IV-tPA (min) | Baseline NIHSS score (0–42) | NIHSS at 24 h after IV-tPA (0–42) | NIHSS at discharge (0–42) | Any ICH (Yes = 1, No = 0) | mRS at 30 days (0–6) |
|-------------------------------|------------|--------------------------------------|-----------------------------|-----------------------------------|--------------------------|--------------------------|----------------------|
| 1                             | 86         | 135                                  | 3                           | 4                                 | 4                        | 0                        | 4                    |
| 2                             | 49         | 111                                  | 9                           | 2                                 | 2                        | 0                        | 3                    |
| 3                             | 50         | 255                                  | 5                           | 0                                 | 0                        | 0                        | 1                    |
| 4                             | 41         | 147                                  | 10                          | 4                                 | 4                        | 0                        | 1                    |
| 5                             | 46         | 115                                  | 7                           | 5                                 | 2                        | 0                        | 2                    |
| 6                             | 65         | 150                                  | 15                          | 14                                | 14                       | 0                        | 4                    |
| 7                             | 72         | 220                                  | 8                           | 9                                 | 5                        | 0                        | 4                    |
| 8                             | 66         | 157                                  | 14                          | 2                                 | 0                        | 0                        | 0                    |
| 9                             | 79         | 137                                  | 5                           | 1                                 | 1                        | 0                        | 0                    |
| 10                            | 67         | 254                                  | 8                           | 0                                 | n/a, expired             | 1                        | 6                    |
| 11                            | 60         | 194                                  | 8                           | 2                                 | 2                        | 0                        | 1                    |
| 12                            | 85         | 168                                  | 11                          | 5                                 | 5                        | 0                        | 4                    |
| 13                            | 62         | 155                                  | 10                          | 2                                 | 0                        | 0                        | 0                    |
| 14                            | 69         | 168                                  | 3                           | 0                                 | 0                        | 0                        | 0                    |
| 15                            | 59         | 129                                  | 6                           | 0                                 | 0                        | 0                        | 0                    |
| 16                            | 47         | 179                                  | 13                          | 9                                 | 1                        | 0                        | 0                    |
| 17                            | 43         | Not recorded                         | 5                           | 0                                 | 0                        | 0                        | 0                    |
improved NIHSS compared to admission. One patient improved initially at 24 h, but subsequently had delayed hemorrhagic transformation and died. Average mRS at 30 days was 1.76, and 11 patients had favorable outcomes (mRS ≤ 2).

Discussion
Intravenous thrombolytics are currently the only approved treatment for patients with acute ischemic stroke. Neuroendovascular treatments such as mechanical embolectomy have demonstrated initial promising clinical results in selected patient cohorts (3,6,7). Tertiary stroke centers with neuroendovascular service typically obtain neurophysiologic imaging studies as part of the stroke work-up in order to identify patients who may be appropriate candidates for mechanical embolectomy. CTP remains a common modality due to its rapid availability, cost effectiveness, and potential for quantitative assessment relative to MRI.

CTP measures cerebral blood volume and mean transit time, and then calculates cerebral blood flow (Fig.1). Large vessel strokes result in perfusion defects that can be detected by CTP. When there is a difference between regional blood flow and blood volume with a corresponding increase in mean transit time, it is termed a mismatch. Mismatch in CTP usually represents the presence of penumbra, or salvageable brain tissue (8). The National Institute of Health stroke scale has also been found to correlate with the severity of stroke but have suboptimal predictive value for large vessel occlusion, and is time-dependent. In one study, a score of 10 has an 81% predictive value for proximal occlusion, but is only 48% sensitive. It also identified 55% of patients with vessel occlusion with a NIHSS less than 10 that are amenable for endovascular

Fig. 1. Images from a patient presenting with symptoms of acute ischemic stroke that subsequently received ivtPA and improved. Clockwise from the top left: non-enhanced CT head, cerebral blood flow map, mean transit time map, cerebral blood volume map.
therapy. Proximal occlusion is found in >90% of subjects with initial NIHSS ≥ 16, and in all of the subjects with NIHSS ≥ 27 (9). Another study also showed that an NIHSS of 7 had 76.2% sensitivity and 70.1% specificity of major vessel occlusion if performed within 6 h of symptom onset (10). In situations where a patient presents with an elevated NIHSS and a negative CTP (no perfusion defect detected), it is often intuitive to reject the use of IV-tPA since there is no perfusion defect for fear of hemorrhagic complications. However, it should be noted that in patients who do not have ischemic stroke, IV-tPA is not associated with elevated risk of intracranial hemorrhage providing the patient does not have other exclusion criteria (5, 11–15).

It is unclear whether the improvement seen in the 13 patients are clearly due to the effect of IV-tPA or the natural history of the disease. Etiology for these deficits may include lacunar strokes in basal ganglia, punctate embolic strokes in the internal capsule, or false negative CTP due to inherent limitations to CTP, including the impact of altered cardiac output, timing of contrast injection, postprocessing, restricted brain coverage, vender-differences in processing algorithms, and the inherent low contrast-to-noise ratio increases susceptibility to artifacts. Nonetheless, the improvements in these patients are significant, objective and measurable. A case-control study or randomized control trial would be of benefit to better classify the effect of IV-tPA and eliminate the possibility of a type 1 error.

In conclusion, our data have clearly demonstrated that there is still a role for IV-tPA in patients with symptoms of acute ischemic stroke despite negative CTP. While further studies are recommended, our current experience supports the use of IV-tPA in eligible patients based on NINDS criteria in patients with negative CTP.

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Conflict of interest

None declared.

Ethical approval

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