Magnetic Resonance Imaging Improves Detection of Intracerebral Hemorrhage Over Computed Tomography After Intra-Arterial Thrombolysis

David M. Greer, MD; Walter J. Koroshetz, MD; Sean Cullen, MD; R. Gilberto Gonzalez, MD; Michael H. Lev, MD

Background and Purpose—Unenhanced CT is routinely performed after intra-arterial (IA) thrombolysis. The presence of residual contrast causing staining of injured brain may mimic intracerebral hemorrhage (ICH). We evaluated MRI with diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI) for detection of ICH after IA thrombolysis, specifically in equivocal areas of hyperdensity seen on postprocedure CT, to help guide the decision to use anticoagulation or antiplatelet therapy after the IA thrombolysis.

Methods—We performed a retrospective analysis of 15 consecutive patients who underwent IA thrombolysis for acute stroke between September 2000 and March 2003. Inclusion criteria required an immediate postprocedure CT with a questionable hyperdensity and, within the next 48 hours, an MRI with DWI and/or SWI.

Results—All patients had CT regions of hyperdensity that were equivocal for the presence of ICH. All patients subsequently underwent DWI, and 11 also underwent SWI. Eleven of 15 patients had magnetic susceptibility-induced hypointensity in DWI hyperintensity regions, signifying the presence of acute deoxyhemoglobin. Nine of these patients also received SWI, which confirmed the presence of blood within these regions. Follow-up CT on all 11 patients confirmed ICH. In the 4 patients without DWI susceptibility change, 0 were found to have ICH on either SWI (performed in 2 patients) or follow-up CT. MRI reliably detected the presence of ICH in all patients, whereas CT failed to differentiate contrast staining from hemorrhage in 4 of the 15 patients.

Conclusions—MRI is an effective means to detect the presence of blood within an equivocal region on post-IA thrombolysis CT. This may influence the decision to use anticoagulation or antiplatelet therapy. (Stroke. 2004;35:491-495.)

Key Words: computed tomography □ intracerebral hemorrhage □ magnetic resonance imaging □ stroke, ischemic □ thrombolysis

Intracerebral hemorrhage (ICH) is one of the most feared complications of acute stroke therapy. With intra-arterial (IA) thrombolysis, the rate of symptomatic ICH (defined as National Institutes of Health Stroke Scale [NIHSS] worsening of ≥4 points) approximated 10% in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial, with a mortality rate in those who hemorrhaged of >80%.

Detection of ICH with conventional CT imaging is limited in the immediate post-IA thrombolysis period as a result of the common presence of angiographic contrast extravasation. Although the hyperdensity in the tissue exceeds that of blood, it is not possible to know whether blood is intermixed with the extravasated dye. A hyperdensity on the postprocedure CT scan that dissipates quickly (over days on serial CT scans) characterizes the hyperdensity as angiographic dye as opposed to blood. Hyperdensity resulting from ICH usually dissipates over weeks or longer. Grading scales designed to approximate the risk for hemorrhage based on CT have been flawed to this point.

It is important in many instances to know in the immediate time frame whether ICH is present or whether the hyperdensity on CT is due solely to angiographic dye extravasation. The implications for decision making include whether to continue or reverse anticoagulation, to continue antiplatelet therapy, or even to administer blood products. Informing the patient and family members about the results of the procedure is also difficult without knowing whether the procedure has been complicated by ICH.

MRI has emerged as a highly sensitive tool for the detection of both chronic and acute hemorrhage. It is well established that when blood extravasates into brain tissue, hemoglobin becomes deoxygenated. Deoxymegoglobin, because of the presence of unpaired electrons, is a paramagnetic substance that produces a local, nonuniform magnetic field, resulting in rapid dephasing of proton spins in T2-weighted imaging.
sequences. Sensitivity for the detection of deoxy-hemoglobin-induced signal loss is greatest for partial flip angle (ie, gradient echo) and echo-planar sequences and is minimal for fast-spin echo T2-weighted sequences, which use multiple 180° refocusing pulses. By distinction, iodinated contrast has no paramagnetic qualities and is thus neutral on susceptibility-weighted imaging (SWI).

Both gradient-echo and low b images obtained from diffusion-weighted echo-planar sequences have been shown to be effective in determining the presence or absence of hemorrhage in numerous studies. To the best of our knowledge, this tool has not been applied in the acute setting in patients immediately after IA thrombolysis. A reliable means of detecting blood in such patients could resolve the uncertainty presented by a hyperdensity on a postprocedure CT scan. We report 15 patients who underwent CT in the immediate postprocedure period, followed by MRI within 48 hours, including diffusion-weighted imaging (DWI) and SWI.

Subjects and Methods
The standard of care for patients arriving at our institution within 6 hours of the onset of an acute neurological event suggestive of an ischemic stroke is a noncontrast CT. If there is no evidence of ICH or of extensive low density suggestive of completed infarction in the region correlating with the neurological deficit, then CT angiography with whole-brain perfusion imaging is performed. A rapid bolus of 120 cm² CT contrast is generally infused in this study. Patients with evidence of occlusion of a circle of Willis vessel with deficits in excess of the low density seen on the noncontrast CT are considered candidates for IA thrombolysis. The risks and benefits of this procedure are discussed with the patient and the family, and informed consent is obtained if there is consensus to proceed. Angiography is performed as quickly as possible for appropriate candidates. In patients who arrive within 3 hours of symptom onset, treatment with IA recombinant tissue plasminogen activator (rtPA) could begin before completion of the intravenous rtPA infusion. Methods of IA treatment include clot manipulation with guide wire, balloon angioplasty, and graded infusion of local rtPA in 1-mg increments (average dose: 4 mg for anterior circulation, 6 to 8 mg for posterior circulation). Excepting postoperative patients and those receiving intravenous rtPA before IA thrombolysis, intravenous eptifibatide is usually administered after the groin puncture to enhance the action of rtPA.

After angiography, regardless of the angiographic recanalization results, patients undergo a noncontrast head CT before transfer to the neurological intensive care unit. In selected patients in whom there is ambiguity regarding the significance of a hyperdensity seen on the CT, we may proceed to MRI. Routine MRI sequences are performed, including echo-planar DWI, echo-planar fluid-attenuated inversion recovery, T1-weighted imaging, T2-weighted imaging, and (in 11 of 15 of our patients) echo-planar T2*-weighted imaging or SWI.

Data Acquisition
Noncontrast CT was performed with a LightSpeed Advantage helical CT scanner (GE Medical Systems): helical mode; 120 to 140 kV; 170 mA; pitch, 0.75; table speed, 7.5 mm/s; and slice thickness, 5 mm. MRI was performed with a 1.5-T unit (Signa, GE Medical Systems) with echo-planar capabilities (Advanced NMR Systems). DWI acquisition parameters were as follows: low b, 0 s/mm²; high b, 1000 s/mm²; DWI pulse sequence with 6 gradient directions; number of excitations, 1; repetition time, 7500 ms; echo time, 73 ms; matrix, 128×128. SWI acquisition parameters were as follows: pulse sequence, multiplanar gradient recalled; repetition time, 750 ms; echo time, 25 ms; skip, 5 mm; slice thickness, 1 mm; and number of excitations, 2.

Institutional Review Board approval was obtained for review of medical records, including all clinical imaging. A stroke neurologist and 2 neuroradiologists retrospectively analyzed all scans performed from September 2000 to March 2003. During that time, a total of 46 patients were treated with IA thrombolysis, but patients without a CT hyperdensity or without a follow-up MRI were excluded from our study, leaving 15 patients for analysis. Each post–IA thrombolysis CT scan was interpreted as showing a hyperdensity, representing dye with or without blood. All MRIs were performed within 48 hours after completion of angiography, and 11 of the 15 occurred immediately after the postprocedure CT scan. The average time between CT and MRI was 15 hours 59 minutes (range, 36 minutes to 46 hours 48 minutes). Reviewers were blinded to the results of the follow-up CT scan.

Patients
See the Table for patient characteristics. There were 7 right middle cerebral artery (MCA) stem occlusions, 5 left MCA stem occlusions, and 3 basilar occlusions. All patients had hyperintensity on postangiographic CT in the territory of the occluded vessel. All underwent MRI with DWI; 11 of 15 also underwent SWI.

Results
All MRIs included DWI (including low b images), and 11 of the 15 also included SWI. DWI on 11 of 15 patients had evidence of hypointense regions within their areas of diffusion-weighted hyperintensity, signifying the presence of deoxyhemoglobin (acute blood) within the area of acute infarction. In these cases, blood was always seen in the brain region that was hyperdense on the postprocedure CT. Serial CT scanning performed >48 hours later demonstrated persistent hyperdensity of blood in all 11 patients. In the remaining 4 patients without susceptibility artifact on DWI or low b imaging, the hyperintensity on the postprocedure CT dissipated over 72 hours, as expected for dye extravasation. The Figure shows the CT, DWI, and SWI scans for 3 patients.

Eleven of the 15 patients also underwent SWI. Nine had areas of hypointensity within the corresponding areas of infarction on DWI and low b imaging, suggestive of acute hemorrhage. These areas matched the areas of hypointensity on DWI and low b images, later confirmed on follow-up CT to be a persistent hyperdensity consistent with hemorrhage. Two patients who underwent SWI showed no areas of hypointensity, and their DWIs and low b images were also negative for hypointensity. None of these patients had a persistent hyperdensity suggestive of hemorrhage on follow-up CT.

Of note, 1 patient who was DWI negative for hypointensity in the area of acute infarction did show areas of low b hypointensity in the subarachnoid region, confirmed to be subarachnoid hemorrhage on follow-up CT imaging.

Another patient who was positive for hypointensity/hemorrhage on both DWI and SWI within the area of infarct also showed areas of hypointensity on SWI in acutely unaffected brain areas (outside of the region of acute infarction). These hypointense regions were seen only on SWI, not on DWI. They were thought to be areas of chronic hemorrhage and were not hyperdense on follow-up CT imaging.

We performed a statistical analysis using McNemar’s test for a case-control study. In this study, there were 4 discordant pairs. There were 4 pair (100%) in whom the control and case had different outcomes and 0 pairs in which the case had an
outcome but the control did not. The 2-tailed probability value was 0.1336 (P = NS).

Discussion
In the present study, we found MRI with SWI to be a sensitive indicator of the presence of hemorrhage within the area of ischemic injury. Given the sensitivity of SWI, multiple areas of microhemorrhages could sometimes be detected, some of which were clearly outside the areas of ischemic injury. They likely represented areas of chronic microhemorrhage because they were often isodense on CT imaging. SWI thus provides a sensitive indication for the presence of hemorrhage, either acute or chronic, in an area that may be in question on a postthrombolysis CT scan, particularly in cases in which there is uncertainty about whether a hyperdensity represents contrast staining, acute hemorrhage, or both.

Furthermore, the presence of marked hypointensity or darkening on DWI and low b imaging was highly sensitive for the detection of acute hemorrhage. All patients with DWI and low b hypointensity within the region of infarction were found to have a persistent hyperdensity on follow-up CT images, consistent with hemorrhage. Taking CT images 3 to 4 days after IA thrombolysis allows sufficient time for contrast "washout," and a hyperdensity seen at that time is indicative of ICH.

In PROACT II, there was a trend toward favorable outcome in patients treated with IA prourokinase for acute stroke compared with the control group that received only intravenous heparin. However, there was a significant increase in the rate of symptomatic intracranial hemorrhage (10% in the prourokinase group versus 2% in the control group).1,7 In a study by Jahan et al,8 hemorrhage

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<th>Patient</th>
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Tob indicates tobacco use; HTN, hypertension; Afib, atrial fibrillation; DM, diabetes mellitus; PVD, peripheral vascular disease; CAD, coronary artery disease; and CVD, cerebrovascular disease.
occurred in 10 of 16 treated patients, 3 of whom had clinical deterioration. Kidwell et al\textsuperscript{10} retrospectively analyzed 89 thrombolysis patients and found that hemorrhage transformation occurred in 29 patients (33%), with minor symptomatic hemorrhage transformation (worsening of 1 to 4 points on the NIHSS) in 10 patients (11%) and major symptomatic hemorrhage transformation (worsening of $\geq$4 points on the NIHSS) in 6 patients (7%). The rate and possibly the extent of ICH in acute stroke patients after thrombolysis may also increase with commonly used therapies. After recanalization of an occluded circle of Willis vessel, concerns about repeated embolization in patients with dissection, extracranial atherosclerotic stenosis, prosthetic heart valves, or diffuse intravascular coagulation may motivate use of anticoagulation. Use of stents to open nearly occluded extracranial vessels as part of the acute intervention and endothelial injury caused by wire or angioplasty balloon manipulation of the clot may provide sites for platelet adhesion with risk of in situ thrombosis. In such cases, a variety of anticoagulant and antiplatelet therapies may be used, including heparin, glycoprotein IIb/IIIa inhibitors, and oral antiplatelet agents. The risk-to-benefit ratio of these therapies may be significantly affected by the presence or absence of ICH.

However, hyperdensity seen on CT imaging after IA thrombolysis is common, and it is not possible to determine whether blood is intermixed with dye in these lesions. Nakano et al\textsuperscript{10} performed a posttherapeutic CT in 77 patients with acute MCA occlusions who were treated with IA thrombolysis. Forty-five hyperdense areas were seen in 33 of 77 patients. In their study, only 29.7% of patients with hyperdense areas had symptomatic hemorrhage. Nakano et al concluded that the absence of hyperdense areas was a reliable negative predictor for symptomatic hemorrhage. Suarez et al\textsuperscript{11} discussed similar difficulties in their study of 54 patients.

Dye staining occurs if dye is trapped in a vasculature that has no egress or if dye extravasates out of the intravascular space into the brain. In the latter case, there is concern that the injured blood vessel will leak blood and dye. However, extravasation of the dye without significant blood can occur, as seen in 2 of 11 patients in our study who were studied with SWI, which is a very sensitive technique used to detect hemorrhage that is below the level of detection on CT.

MRI has emerged as an excellent modality for the detection of ICH. Numerous studies have shown the utility of SWI in detecting both acute hemorrhage and chronic, perhaps silent, microhemorrhages.\textsuperscript{3,4,12–15} SWI is likely to be more sensitive to the presence of chronic hemorrhage with iron deposition in the brain and to the presence of calcification. However, a region of very low signal intensity on low $b$ imaging within a region that is hyperintense on DWI may be highly specific for acute hemorrhage within a zone of ischemic injury.

MRI has been used only sparingly in the IA thrombolysis setting to evaluate for hemorrhage. Kidwell et al\textsuperscript{6} used pretreatment SWI to determine the presence or absence of microhemorrhages before IA thrombolysis in an attempt to determine whether these patients had an increased rate of ICH. However, to the best of our knowledge, no studies have looked at the immediate postprocedure period with MRI to determine the presence or absence of new ICH.

There are several potential sources of bias in this study. First, this was not a prospective or randomized study, and although all patients routinely undergo postprocedure CT imaging, the decision to have the patient undergo MRI is at the discretion of the treating physicians. That decision may be influenced by uncertainty regarding the contents of an area of hyperdensity or the use of postprocedure antplatelet or anticoagulation therapy, or MRI may be performed for other indications such as determining the final infarct volume. Second, many patients, with or without hyperdensity on postprocedure CT, did not undergo MRI; thus, we also present a selected group from our overall stroke population. Finally, the number of patients in the study was small and not statistically significant. Further prospective studies are warranted in a larger patient population.

Despite these limitations, the data included here may immediately affect practice in those centers providing IA thrombolysis.

In summary, these data demonstrate that MRI is a clinically useful tool for detecting hemorrhage in the immediate post–IA thrombolysis period in patients with a hyperdense lesion on CT. The question of whether blood is included in the hyperdense CT lesion or whether it is only dye can be answered immediately with MRI but otherwise requires serial CT scanning over several days. Answering this question in the immediate postthrombolysis period may have clear clinical significance. Future controlled studies are needed to better define the sensitivity and specificity of MRI for detecting postthrombolysis hemorrhage and, more importantly, its value in improving outcome in the postthrombolysis patient.

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