Neuroimaging markers of hemorrhagic risk with stroke reperfusion therapy

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ABSTRACT

Objective: We sought to identify pretreatment neuroimaging markers associated with intracerebral hemorrhage (ICH) after reperfusion therapy for acute ischemic stroke.

Methods: A literature review using available online medical literature databases was performed to identify noninvasive imaging markers correlated with ICH after reperfusion therapy. Key words, including different neuroimaging modalities such as noncontrast CT, multimodal CT, and MRI techniques, were queried. The review included randomized, controlled trials, post hoc studies, and institutional registries. Studies of IV as well as intra-arterial reperfusion therapies were considered. Articles were organized on the basis of imaging modality and type of treatment. Each imaging modality was given 1 of 3 grades for consideration of use in clinical practice (grade 1: a modality whose use for hemorrhage prediction is supported by randomized controlled trials or post hoc studies from prospective trials; grade 2: a modality that is largely available but requires further prospective validation; and grade 3: a modality which is rarely used and has limited clinical utility).

Results: Grade 1 imaging modalities included the size of infarction as seen on noncontrast CT or diffusion MRI. Higher hemorrhagic risk has been seen with larger infarctions, suggesting that these imaging modalities may be effective screening tests to exclude specific patients. Perfusion imaging using CT or MRI was considered to have a grade 2 recommendation, pending further validation. The use of xenon CT, radionuclide imaging, voxel-based MRI analysis, and blood–brain barrier disruption imaging still require further design improvements (grade 3).

Conclusions: Future reperfusion trials require clearly defined protocols for imaging and determination of symptomatic ICH. Future trials may consider the use of perfusion imaging and the inclusion of patients without large territorial infarctions to accurately predict those at risk for ICH with reperfusion therapy. *Neurology*® 2012;79 (Suppl 1):S100–S104

GLOSSARY

ADC = acquired diffusion coefficient; **ASPECTS** = Alberta Stroke Program Early CT Score; **BBB** = blood–brain barrier; **CBF** = cerebral blood flow; **CBV** = cerebral blood volume; **DEFUSE** = Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution; **ECASS** = European Cooperative Acute Stroke Study; **FLAIR** = fluid-attenuated inversion recovery; **HARM** = hyperintense acute reperfusion marker; **HI** = hemorrhagic infarction; **IA** = intra-arterial; **ICH** = intracerebral hemorrhage; **MCA** = middle cerebral artery; **NINDS** = National Institute of Neurological Disorders and Stroke; **PH** = parenchymal hematoma; **PROACT** = Prolyse in Acute Cerebral Thromboembolism; **PWI** = perfusion-weighted imaging; **tPA** = tissue plasminogen activator; **XeCT** = xenon-enhanced CT.

Intracerebral hemorrhage (ICH) is the most feared complication of IV and intra-arterial (IA) ischemic stroke reperfusion therapy. Whereas neuroimaging modalities can select ideal IV and IA treatment candidates, these tools may also have a role in identifying those at risk of hemorrhage.

Our aim was to perform a literature review of IV and IA reperfusion studies, focusing on neuroimaging markers associated with post-reperfusion ICH.

METHODS We performed a review of the medical literature, using indexed online searches of MEDLINE and PubMed. Studies were considered from the period January 1994 to December 2011. Key terms or phrases were searched for studies describing noninvasive imaging modalities associated with ICH after IV or IA reperfusion therapy. Study types included randomized controlled trials, prospective registries, post hoc analyses of prospective studies, and institutional registries.

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Articles were organized on the basis of imaging modality and type of treatment. Each imaging modality was given 1 of 3 grades for consideration of use in clinical practice (grade 1: a modality whose use for hemorrhage prediction is supported by randomized, controlled trials or post hoc analyses from prospective studies; grade 2: an available modality studied as part of a retrospective institutional series and requiring further prospective validation; grade 3: a modality that is uncommonly used and has limited clinical utility).

RESULTS **Definitions.** Unfortunately, the definitions of hemorrhage post-reperfusion therapy are heterogeneous, limiting the ability to make direct comparisons between each treatment and imaging modality. In the National Institute of Neurological Disorders and Stroke (NINDS) trial, the symptomatic hemorrhage rate was 6.4%, and in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial, 10%.[1,2] However, the definitions used in these 2 studies were different. The NINDS trial defined symptomatic hemorrhages as any new parenchymal hyperdensities on serial CT scans with any neurologic deterioration.[1] In PROACT II, symptomatic hemorrhages had to coincide with a 4-point increase in the stroke score or decline in level of consciousness.[2] Since then, recent studies have attempted to combine the presence of CT scan hyperdensities with an objective measure of neurologic deterioration, as in PROACT II.[3] Still, more objective definitions of hemorrhage have been derived from European thrombolytic studies correlating the amount of hemorrhage and size of infarction.[4]

In a post hoc analysis of the European Cooperative Acute Stroke Study (ECASS) II, a radiologic definition for ICH was proposed: hemorrhagic infarction, described as petechial hemorrhages within a hypodensity, and parenchymal hematomas (PHs) were hemorrhages extending beyond the hypodensity with varying amounts of mass effect. In a multivariate analysis, only PH type 2, those hematomas >30% in size of the CT hypodensity and with mass effect, were found to be significantly correlated with neurologic deterioration at 24 hours and death at 3 months.[5] This scheme has been adopted by subsequent IA trials and registries to implicate the hemorrhagic complication as the cause for neurologic decline.[6–8]

Noncontrast CT. Higher hemorrhage rates were seen in ECASS I, largely due to the inclusion of patients with large hypodensities >1/3 of the middle cerebral artery (MCA) territory on baseline CT, although the use of a higher-dose (1.1 mg/kg) tissue plasminogen activator (tPA) regimen may also have played a role.[9] Recognition of this led to stricter monitoring and exclusion of such patients in the NINDS trial, which is believed to have contributed to a lower symptomatic hemorrhage rate. Given the exclusion in the NINDS study, subsequent IA studies, including PROACT II, also excluded those with large hypodensities >1/3 of the MCA territory.[2]

A post hoc analysis of baseline noncontrast CT scans in the NINDS trial, however, did not define any radiologic appearance linked to ICH.[10] Analysis of the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) also failed to show a relationship between ischemic changes and symptomatic PH type 2.[8] Hence, early ischemic changes on CT may not preclude the use of thrombolytics, but caution has been suggested when these changes appear to encompass a large area of parenchyma.

An objective scale for identifying patients with ischemic changes in greater than 1/3 of the MCA territory is the Alberta Stroke Program Early CT Score (ASPECTS).[11] A score of <7 has best correlated with those patients who have >1/3 of MCA hypodensity, with good inter-rater agreement.[12] Hence, the ASPECTS tool has been validated and can be used to withhold thrombolysis for those who would not have been enrolled in the NINDS study because of their baseline CT changes. However, less extensive CT changes may not predict benefit from IV tPA, as demonstrated in a pooled analysis of IV trials.[13]

A post hoc study of the PROACT II data found a trend toward correlation between low ASPECTS scores and higher symptomatic hemorrhage rates (8.7% in the >7 group and 15.3% in the <7 group; relative risk, 2.2 [0.5–9.6]).[14] A similar finding was noted with the use of ASPECTS in combined IV and IA tPA treatment.[15] The consistency of these findings suggests that the extent of early infarction should be considered before systemic or IA thrombolysis and that the ASPECTS score is an objective tool for this measure (grade 1).

CT physiologic data. In the absence of CT hypodensity, symptomatic hemorrhages still occur. Perfusion CT modalities may offer insight into physiologic changes during ischemia-predisposing ICH. Three techniques have been studied within small, single-center, retrospective registries prior to IA therapy: SPECT, xenon-enhanced CT (XeCT), and CT perfusion. The definitions of symptomatic hemorrhage are not uniform, making comparison difficult. However, they do reveal insights into physiologic parameters that may be associated with reperfusion hemorrhage.

SPECT is a nonquantitative technique measuring relative differences in cerebral blood flow (CBF). A radionuclide tracer is tagged to a compound, which is given IV and diffuses across the blood–brain bar-

rier (BBB) into neurons and glial cells. Tracer activity, which correlates with CBF, is measured in both hemispheres. Ischemic regions are defined as areas of low activity in comparison with the contralateral hemisphere or cerebellum.[16]

In a study of patients treated with IA thrombolytics, 20 patients underwent pretreatment SPECT with 99mTc-labeled hexamethylpropyleneamine oxime. Hemorrhagic transformation occurred in 5 patients, although no mention is made of how many were symptomatic. All patients with a hemispheric ischemic regional activity ratio of <0.35 in comparison with the cerebellum developed ICH after treatment, suggesting that those with significant reductions in CBF despite normal CT findings were at risk for hemorrhage.[17] The small size of this study, poor ICH classification, and logistical challenges of SPECT in the acute setting limit the use and understanding of this technique (grade 3).

Similarly, XeCT quantitatively measures CBF and has been used to determine hemorrhagic thresholds with IA therapy. Xenon is an inhaled anesthetic with the same density as iodine. As xenon diffuses across the BBB during sequential CT scanning, the change in Hounsfield units equates absolute CBF.[16] Of 23 patients undergoing IA thrombolysis and receiving a baseline XeCT prior to treatment, 5 (22%) were found to have a symptomatic PH (4, PH type 2; and 1, PH type 1). In the multivariate analysis, those with a mean ischemic hemisphere CBF <13 mL/100 g/min were at highest risk for developing PH. There was no statistical difference in baseline ASPECTS between those who developed PH and those who did not, suggesting that low CBF is a physiologic parameter, in addition to frank infarction, which may predispose to ICH.[18] Although this series did define the ICH complication and attempted to correlate XeCT with noncontrast CT, the size is small, and XeCT is no longer available for acute diagnostics (grade 3).

CT perfusion is more widely available for use than the physiologic modalities already discussed and has been used for ICH prediction. Current postprocessing software allows mean values of cerebral blood volume (CBV), mean transit time, and CBF to be obtained within regions of interest drawn in the MCA territory. A retrospective, multicenter registry of 57 patients receiving IA therapy concluded that baseline mean CBV predicted the development of ICH, particularly when the mean MCA CBV is <1.8 mL/100 g.[19] CBF was not as strong a predictor of ICH as it was with XeCT, perhaps because CBF is a derived value from deconvolution of mean transit time and CBV. Hence, CT perfusion CBV may be a better predictor of ICH. However, reproducibility of results and prospective validation are lacking (grade 2).

MRI detection of acute hemorrhage. CT has long been thought to be the gold standard in detecting acute ICH. However, this assumption was challenged by the early use of MRI at the time of stroke presentation.[20] Early MRI use identified 22 of 26 patients with acute ICH and was more sensitive than CT in detecting early changes of hemorrhagic transformation. This capability holds promise for selecting better candidates for endovascular procedures.

In addition to the accuracy of MRI in detecting frank hemorrhages, the technique has proven significantly more sensitive in detecting microbleeds on gradient-echo imaging. These small areas of gradient-echo positivity are of questionable clinical significance for consideration of IV thrombolysis and have yet to be identified as an exclusion criterion for IA therapy.[21–23] A formal comparison of noncontrast CT against MRI is needed to determine if the latter is a better screening tool (grade 2).

MRI as a marker for BBB disruption. Gadolinium-enhanced MRI has been suggested as a tool capable of identifying areas of BBB disruption, which may increase the vulnerability to hemorrhagic transformation in the setting of ischemia.[24] This phenomenon has been described as a hyperintense acute reperfusion marker (HARM) and was found in a subset of subjects undergoing magnetic resonance perfusion imaging with gadolinium in the setting of acute stroke. The finding was evidence of sulcal hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequences when acquired after gadolinium administration. HARM was associated with a higher risk of hemorrhagic transformation and poor neurologic outcome.[25] A retrospective review of 144 acute stroke patients with baseline and subacute post-gadolinium FLAIR MRI imaging was performed. Of these, 38 received thrombolytic therapy (35 IV and 3 IA). HARM was observed in 47 patients (33%) within 12.9 hours after stroke onset. The risk of hemorrhagic transformation was higher in those with the HARM finding (73% in those with HARM vs 25% in those without; $p < 0.001$) at a mean time of 31.3 hours after stroke onset. The HARM MRI finding, however, has not been correlated with symptomatic hemorrhages but rather with an increased risk of asymptomatic hemorrhagic infarction. Furthermore, HARM is not a baseline finding but rather observed with serial MRI after treatment. Despite these limitations, this technique may identify patients who need tar-

geted blood pressure and glycemic control after reperfusion therapy (grade 3).

MRI diffusion-weighted imaging. Acquired diffusion coefficient (ADC) from diffusion MRI can be analyzed to determine the density of MRI voxels.[26] A retrospective series of 17 stroke patients, some of whom received thrombolytic therapy, underwent a baseline diffusion MRI within 8 hours. Those with ADC maps containing voxels with a low diffusion rate were more likely to develop hemorrhagic transformation, although types of ICH were not specified. Overall, 40% of ADC voxel values $\leq 500 \times 10^{-6}$ mm^2/s resulted in hemorrhage, although only 1 patient became symptomatic.[27] These findings were replicated in another retrospective study of 29 patients receiving IV tPA and undergoing baseline diffusion MRI. The low ADC values have been postulated to represent areas of irreversible microvascular injury from ischemia and were found in this study to correlate with increase risk of post-thrombolysis ICH, although no differentiation was made between types of hemorrhage.[28] However, this voxel-based analysis focuses on small ischemic regions and does not predict PH type 2, which is thought to be of the most clinical significance (grade 3).

A better use of diffusion MRI appears to be a volumetric measurement of infarcted tissue. Similar to the use of CT ASPECTS, the extent of infarction correlates with hemorrhagic risk. A post hoc analysis from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study and other similar registries identified a statistically significant increase in risk of symptomatic hemorrhage, defined as any bleeding associated with a 4-point increase in the stroke score, associated with the infarct lesion size[29,30] (grade 1).

Perfusion-weighted MRI. Perfusion-weighted imaging (PWI), like other perfusion imaging techniques, is generally used to identify ischemic territories at risk for impending infarction. However, an interim analysis from the DEFUSE study indicated that not all patients with a perfusion–diffusion mismatch are suitable for reperfusion therapy and identified those at risk for ICH.[30] In this study, patients with acute stroke between 3 and 6 hours from symptom onset were treated with IV tPA. Prior to treatment, patients underwent a diffusion–perfusion MRI. PWI was done with dynamic susceptibility after an IV gadolinium bolus. Hypoperfused regions were defined as those MRI voxels with a $T_{max} \geq 2$ seconds, referring to the time lag for the ischemic hemispheric signal to reattenuate, reflecting impaired gadolinium, or blood flow, delivery. An interim analysis identified that patients with large DWI volumes (≥100 mL), large infarcts such as those seen in ECASS I, and large PWI volumes (≥100 mL) with a $T_{max} \geq 8$ seconds were more likely to experience an ICH with successful reperfusion[30] (grade 2).

SYNTHESIS With the growing use of varied imaging techniques in acute stroke, predictors of hemorrhagic complications and risks to reperfusion therapy are being identified. However, the lack of uniform definitions for hemorrhage and treatment protocols makes comparisons among existing studies difficult. Although no study has identified a specific imaging parameter which negates the benefit of IV thrombolysis, a common theme, with either systemic or IA thrombolysis, is to avoid treatment in patients with large infarctions, seen on CT or diffusion-weighted MRI.

Perfusion imaging has shown promise in the prediction of salvageable brain tissue in ischemic stroke and also in hemorrhagic risk prediction. Studies with CT perfusion and PWI suggest that large areas of ischemic tissue are also at risk for reperfusion hemorrhage. With these early studies, prospective validation is needed to determine if these techniques can identify the highest-risk patients and prevent poor outcomes, as noted in recent reviews.[31,32] Future clinical trial designs will require uniform definitions for symptomatic ICH, such as PH, and a pretreatment imaging and treatment protocol for meaningful results.

AUTHOR CONTRIBUTIONS

Dr. Edgell: drafting/ revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Vora: drafting/ revising the manuscript, study concept or design, contribution of vital reagents/tools/patents, acquisition of data.

DISCLOSURE

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