Early Ischemic Signs Should Not Be Used as Exclusion Criteria in Thrombolysis Trials

To the Editor:

I read with great interest the article by Higashida and colleagues on the trial design of studies to test intra-arterial thrombolysis. The authors are to be congratulated for their prodigious efforts to set standards for intra-arterial thrombolysis trials. Unfortunately, the evidence for using one of the traditional exclusion criteria should no longer be considered binding. The criterion in question is based on the ECASS trials on intravenous thrombolysis and excludes patients with “an acute hypodense parenchymal lesion on CT or effacement of the cerebral sulci in more than one-third of the MCA territory or suspected stroke region.”

Recent evidence from a retrospective analysis of the NINDS data, however, showed that patients with early ischemic signs in more than one third of the above regions reacted even better to thrombolysis and it benefited most. Using the ASPECTS grading of stroke CT, Hill and colleagues in contrast reported that patients with larger initial early ischemic signs benefited less from intra-arterial thrombolysis with pro-urokinase. Of course, intra-arterial thrombolysis is obviously different from intravenous thrombolysis, and not all findings relevant for one type are relevant for the other. But the exclusion of the above patient group will not only restrict the usage of this therapy but, most importantly, prevent those patients from receiving it who may well benefit. Therefore, I advise against using this criterion for patient selection at this time.

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Response

Dr Hamann suggests that CT hypodensity in more than one third of the middle cerebral artery (MCA) territory using the European Cooperative Acute Stroke Study (ECASS) CT criterion should not be used as an exclusion criterion for intra-arterial, and presumably intravenous, thrombolysis trials. The predictive value of hypodensity on CT is not only time dependent, but also volume dependent and location dependent. Hypodensity <3 hours may not represent the same pathology as hypodensity >3 hours; perhaps hypodense tissue <3 hours remains somewhat salvageable in some patients. However, as time goes on, the ability to salvage hypodense brain tissue on CT becomes less and the risk of hemorrhage increases. Other variables including age, baseline stroke severity, and collateral circulation also influence the predictive value of CT hypodensity. In the National Institutes of Neurological Disorders Stroke (NINDS) trial CT analysis, there were very few patients with ECASS CT violations—not unexpected with a <3-hour time window for treatment. The NINDS CT analysis was therefore not powered to detect such interactions. However, the frequency of ECASS CT violations increases over time. Indeed, extensive hypodensity on the initial CT brain scan should prompt the investigator to question the true time of stroke onset or it may suggest very poor collateral circulation to the area of ischemia.

Interpretation of CT hypodensity is subject to tremendous interobserver variability, especially in a community hospital setting. The definition of “one third of the MCA territory” is imprecise as are the more subtle early signs of infarction such as “sulcal effacement.” In a separate CT analysis of the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT II), the outcome in patients with early CT hypodensity >100 mL was universally poor. In addition, 50% of ECASS CT violators in PROACT II showed hemorrhagic conversion on the 24-hour follow-up CT brain scan. ASPECTS attempts to improve on the ECASS CT criterion by incorporating location into a hypodensity score. The ASPECTS analysis of PROACT II pointed out that CT hypodensity becomes more clinically important with time. All 12 patients who were ECASS violators in PROACT II had ASPECT scores ≤7. Patients with ASPECT scores ≤7 did not benefit from intra-arterial thrombolysis and had higher rates of mortality and symptomatic brain hemorrhage compared with the control group.

For all of these reasons, we agree that early CT hypodensity by itself is a relatively crude predictor of outcome after brain infarction. New imaging techniques such as CT perfusion and diffusion-weighted/perfusion-weighted MRI will likely increase the predictive power of early ischemic changes. However, pending the validation of these new imaging techniques we continue to recommend excluding patients with frank and obvious CT hypodensity in more than one third of the MCA territory from clinical thrombolysis trials >3 hours. In thrombolysis trials <3 hours, the issue is less settled. As in ECASS and PROACT II, CT scans should be read in a blinded fashion by an experienced and well-trained physician, following a standardized methodology. The predictive value of early CT hypodensity can be increased by excluding patients with hypodensity >100 mL of brain tissue at risk, or patients with an ASPECTS score ≤7. If such patients are included in a clinical thrombolysis trial, they should be stratified and a different outcome analysis applied, as the likelihood of detecting clinical efficacy is low.

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