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Intraarterial Thrombolysis for Cerebral Infarction:To Treat or Not to Treat, and How?

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contained within a less restrictive matrix with fewer macromolecules, allowing greater freedom of motion and consequent loss of signal on diffusion-weighted images. In addition, susceptibility effects from blood products (not appreciated on fast spin-echo T2-weighted images) may result in greater signal dephasing on echo-planar images. Desprechins et al state that abscesses had ADC values approximately 50% lower than infarcts. This observation, while interesting, is not clinically critical because differentiating between an abscess and an infarct is usually not difficult.

Now that we know that diffusion-weighted imaging is useful in the preoperative diagnosis of abscesses, what else is available? At our institution, we have used proton MR spectroscopy (HMRS) for this purpose with a high degree of success. The presence of lactate and lipids is not pathognomonic for abscesses but may be seen in necrotic tissue regardless of its etiology. The presence of acetate, succinate, and cytosolic amino acids is, however, highly suggestive of an abscess. Unfortunately, HMRS requires, at the least, an additional 10 minutes to perform and some patients with cerebral abscesses are very sick and unable to remain still. Gadolinium-perfusion MR imaging also may be performed when trying to differentiate an abscess from a tumor. Calculated relative cerebral blood volume (rCBV) is significantly lower in toxoplasmosis when compared to normal brain, whereas rCBV is elevated in tumor (3). Performing perfusion studies not only requires an echo-planar MR unit but also a power injector (which costs approximately $30,000) and extensive postprocessing of data. Fluid-attenuated inversion recovery images (FLAIR) may be helpful in distinguishing fluid-filled lesions. Lesions containing CSF or CSF-like fluid have low signal intensity whereas lesions containing necrosis, as a consequence of inflammation or tumor, show different characteristics. FLAIR images may be obtained in only 3 to 4 minutes and therefore do not result in a significant prolongation of the examination. If one substitutes FLAIR for T2-weighted images, it is not clear if some specificity (such as the low signal intensity of abscess capsule) will be lost. In reality, many of us use the proton-density images to increase the specificity of our differential diagnosis of cystic lesions. The utility of postcontrast FLAIR images also needs to be determined. Although FLAIR may help differentiate simple cysts from ones with a more complex content, it does not enable separation of an abscess from a necrotic tumor as effectively as diffusion-weighted imaging.

So, given all of these techniques to choose from, what should be done when an abscess is being considered? I prefer diffusion-weighted imaging in combination with routine contrast-enhanced MR imaging. Are ADC maps absolutely necessary? From a purely practical and clinical standpoint, I would have to say, probably not. Trace diffusion-weighted imaging, which may be generated in most units with software provided by the manufacturer, has only a very low degree of contamination from T2 relaxation that affects and provides valuable information regarding diffusion properties of a lesion. The information obtained from diffusion-weighted imaging, combined with a thin rim of low signal intensity on T2-weighted images that enhances in a smooth and homogeneous fashion, should place abscess as the foremost consideration. Although other sequences are available, I tend to choose those that are easiest to perform and, at this time, I believe that diffusion-weighted imaging and routine contrast-enhanced MR imaging are easy to obtain and interpret.

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Intraarterial Thrombolysis for Cerebral Infarction: To Treat or Not to Treat, and How?

The appeal of intraarterial thrombolysis is hard to resist. After spending the last 3 decades watching our cardiologist colleagues save patients from death's door with acute intervention, it appears that it's finally our turn to apply some of these techniques for the benefit of some of the 500,000 new acute stroke patients seen each year. The development of microcatheters, the approval of intravenous tissue plasminogen activator (rt-PA) for acute stroke, and the recent encouraging trial of intraarterial prourokinase has created a palpable new enthusiasm among neuroradiologists and neurologists who finally feel that they can provide something more than supportive care for many of these patients. But who should be treated and, importantly, who should not?

In this issue of the *AJNR*, Jahan et al (page 1291) report the outcome in 26 patients with acute cerebral infarction in whom intraarterial urokinase was used for thrombolysis within 6 hours after the onset

of symptoms. The authors succinctly review the pertinent issues and beautifully summarize the literature to date on this topic. For this alone, the article is worth the read. Although no control group was used, their results closely parallel those reported in the placebo-controlled, double-blinded, multi-institutional intraarterial prourokinase study reported by del Zoppo et al (1) and the National Institute of Neurologic Disorders and Stroke (NINDS) intravenous rt-PA trial (2). Jahan et al report that successful reperfusion was achieved in 42% of their patients and that these patients had a better outcome than those in whom reperfusion was unsuccessful. A good outcome, as measured by a Rankin score of 0–1, was achieved in 28.6% of their patients as compared with 30.8% of the treated patients and 21.4% of the placebo group in the Prolyse in Acute Cerebral Thromboembolism (PROACT) trial. Defining a good outcome as a Rankin score at 1 year of 0–2, 48% of Jahan's group had a good outcome compared with 41% in the NINDS intravenous rt-PA study. Jahan's group included patients with internal carotid artery (ICA) and middle cerebral artery (MCA) occlusions who had lower average National Institutes of Health Stroke Study (NIHSS) scores at outset than those in the PROACT I trial. Because time to treatment was probably longer than in the rt-PA trial, which for all purposes was a 0–3-hour trial, this is reasonably good outcome data. Poor outcome or death was associated with nonrecanalization, older aged patients over 70 years old, left hemispheric stroke, and ICA bifurcation lesions. The incidence of hemorrhage transformation was 38% in Jahan's group, 12% of whom had a symptomatic hemorrhage, which was twice that of the NINDS study and the low-dose heparin group of the PROACT trial, but equal to the overall PROACT hemorrhage rate. They also noted that this incidence is not statistically different from that of the placebo group of PROACT or that reported in untreated patients. The rate of hemorrhage is related to the dose of urokinase or heparin, and probably also to the presence of lenticulostriate occlusion, which does not have collateral pathways and therefore usually sustains endothelial damage. These results are welcome news that another trial, albeit without a control group and including ICA and MCA lesions, showed results similar to rt-PA and intraarterial PROACT therapy. But it also raises significant questions. Which agent or technique should be used? Who should be treated? Certainly intravenous rt-PA is easier to deliver than intraarterial therapy, but is associated with systemic doses and is not focused at the site of the thrombus. Intraarterial therapy has the advantage of being site-specific, but requires expertise in catheter placement in the MCA not readily available in all facilities, or by the number of neuroradiologists who might be needed to perform these maneuvers at odd hours of the night. It is also expensive and time-consuming. The results presented are not overwhelmingly in support of intraarterial treatment, and a controlled study of the two techniques begs to be done to settle this issue.

Who should not be treated? This is also a difficult question to answer. Although Jahan and colleagues found no significant relationship between the size of a CT hypodensity in the MCA territory and poor outcome or hemorrhage, others have shown such a relationship in larger cohorts than that studied by Jahan. Von Kummer et al found that CT hypodensity covering more than 50% of the MCA had an 85% positive predictive value for fatal clinical outcome after treatment with rt-PA of doses between 30 mg and 100 mg (3). Similarly, in the European Cooperative Acute Stroke Study (ECASS), the severity of initial clinical deficit and the presence of early ischemic changes on CT scans were associated with increased risk of hemorrhagic infarction. Angiographic predictors of the risk of hemorrhage have not been emphasized. Fukazawa and colleagues (4), however, found that arterial shunting in the territory supplied by the lenticulostriate arteries was present in 7 (70%) of 10 who subsequently hemorrhaged in the basal ganglia after thrombolysis, whereas this finding was not seen in any of the patients in the nonhemorrhagic group. Unfortunately, Jahan et al do not detail any angiographic findings predictive of subsequent hemorrhage or outcome. It would be very useful to have an indicator, determined either clinically or by CT or angiography, of the relative risk of hemorrhagic transformation prior to thrombolytic therapy. These patients then could be excluded from therapy and possible harm. Certainly it seems logical that those with hypodensity involving the basal ganglia region may be at higher risk of hemorrhage and should be assessed carefully for those points that might exclude them from consideration for thrombolysis.

Finally, a word must be said for the insensitivity of CT to areas of infarction. It has been our experience, as the central reading laboratory for the PROACT trial, that most patients (over 70%) entering the hospital with an acute cerebral infarction in the MCA territory show abnormality on CT scans. This also has been the experience of von Kummer. Nevertheless, many patients have subtle areas of low density that clearly extend to involve a larger region of the brain within 24 hours of admission. These areas were most likely destined for infarction at onset, but were not visible on CT scans. Diffusion MR imaging has supported this observation. After therapy, no patients in the PROACT trial with a low-density region at onset returned to normal. Therefore, one can assume that a CT-revealed hypodensity at onset represents irreversible infarction in most cases. Furthermore, many of the patients entered into thrombolytic trials had larger areas of infarction than could be appreciated with initial CT. Perfusion and diffusion MR imaging would be the ideal manner to estimate the more accurate volume of infarcted tissue at onset of stroke, as well as the tissue at risk. The difference between these two volumes would

be the ideal way to estimate those who might well benefit from thrombolysis. These techniques are probably impractical for a larger multicenter trial at the present, but as this technology matures, this would seem a more optimal manner in which to stratify patients into groups that would benefit from thrombolysis from those who have little tissue left at risk.

Thus, we are still left with a few incompletely answered questions: Which technique should be used and in whom? Why do some patients recanalize and others not? Why do some patients hemorrhage and others not? What features are more predictive at the initial onset of stroke for who will hemorrhage after thrombolysis? Most importantly, are we prepared to meet the demand of these new interventional techniques on a large scale?

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