Is It Ethical to Have a Placebo Arm in Reperfusion Trials in the 3- to 6-Hour Time Window? No Time Frame or Time Gain?

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The rigid and narrow time window of 3 hours for thrombolytic therapy is arguably the single most important factor that hampered the wider use of this death- and disability-reducing therapy over the past decade. However, systemic thrombolysis is still the only approved treatment for acute ischemic stroke. This leads to the fact that expanding the time window for thrombolysis is among the most important and extensively studied topics in current research on the treatment of acute ischemic stroke. In recent years, especially with the introduction of multiparametric stroke MRI techniques, enough progress has been made in clinical practice that with the present knowledge and experience it would be ethically problematic to expose patients to the risk of receiving placebo in a trial within the 3- to 6-hour time window.

How sure can we be about the 3-hour time window anyway? It is obvious that it is derived from a single study only, the NINDS trial. Although one must not forget the fact that this is still the only positive trial, had the endpoints of NINDS been applied to the first ECASS trial, we probably would not have this present controversy. Furthermore, one might consider this whole controversy moot because the pooled analysis by Hacke et al., demonstrates a treatment effect up to 4.5 hours, and the meta-analysis by Wardlaw et al demonstrates a treatment effect up to 6 hours, thus formally providing level 1 evidence (meta-analysis of randomized control trials) even in patients selected by "only" noncontrast CT. During the past few years, multiparametric MRI techniques using the PI/DWI mismatch concept have been introduced into clinical practice to select patients for thrombolysis or other recanalization therapies in the extended time window. The rationale behind the MRI approach is to substitute the time window with an individual tissue window defined for the single patient based on imaging findings. Recently, a study showing proof of principle for using the PI/DWI mismatch has been published. DEFUSE recruited patients treated within 3 to 6 hours after symptom onset based on CT findings. An MRI was obtained immediately before and after recombinant tissue plasminogen activator. Only patients with a mismatch benefited from thrombolysis, whereas others did not. The recently published EPITHET study was very similar but randomized patients to recombinant tissue plasminogen activator or placebo. Being a phase II study, this trial was clearly underpowered to show significant efficacy results. Patients in the recombinant tissue plasminogen activator arm had a trend toward a reduced infarct growth and a significantly higher chance for reperfusion, which itself was an important predictor for a favorable outcome. Rates of symptomatic intracranial hemorrhage were comparable to those of the 3-hour trials. Two placebo-controlled phase II trials, the DIAS trial and DEDAS trial, using the thrombolytic desmoteplase, have been conducted in a time window of 3 to 9 hours, applying the MRI mismatch selection process. Besides a clear efficacy signal, these trials again demonstrated that the therapy was safe. Although the follow-up DIAS-2 trial failed to show efficacy, safety of treatment again was not a problem (ESC, Glasgow 2007).

Demonstrating that MRI-based thrombolysis, although being "off-label," is rather a routine clinical practice than an experimental therapy in dedicated stroke centers; recently, 3 large observational studies using stroke MRI in an extended time window have been published, thus providing at least level 3 evidence. Thomalla et al., compared outcome and symptomatic bleeding complications of intravenous recombinant tissue plasminogen activator within 6 hours in MRI-selected patients with the pooled data of the large stroke trial. In a third study, Schellinger et al. analyzed the data of 1210 patients pooled from databases of 5 European sites that use MRI-based selection algorithm in an extended time window. In all studies, safety and clinical outcome of patients with MRI-based treatment beyond 3 hours were at least comparable to the ones of patients with CT-based treatment within 3 hours. Furthermore, in all those MRI-based studies, time from onset to treatment was neither a treatment effect-modifying factor nor a safety factor.

The safety profile is important information when it comes to the core ethical question of the use of placebo in future
trials. Why withhold a potentially effective treatment when it was shown to be safe and there is no other option available? What exaggerates the ethical dilemma for using placebo is that with modern imaging techniques, one now has the comprehensive information on the individual patient’s situation. In the acute setting, one is hard-pressed to (potentially) withhold therapy from a patient with an embolic M1 occlusion, a corresponding large perfusion—with a so far small diffusion—lesion. After it was shown over and over again that recanalization is a prerequisite for a favorable outcome and that thrombolysis facilitates recanalization, how much more sure do we need to be that this patient’s brain really needs blood supply? Do we want to test it by giving this patient a 1-hour saline infusion? No! What if we conduct a placebo-controlled trial and the effect size at the end turns out to be smaller than expected and the trial fails to show significance? Does that mean we should not treat those patients at all? We do have a treatment that makes sense from a pathophysiological standpoint and that was shown to be safe and effective in multiple series in routine clinical practice. There are established therapies in neurology that are less proven. It would take hundreds of additional placebo patients to be “euthanized” to conduct another large clinical trial. Is this really the way to go? We believe not.

Disclosures
M.K. and S.S. received travel grants from Boehringer Ingelheim. S.S. is a member of the speaker’s bureau of Boehringer Ingelheim, the manufacturer of recombinant tissue plasminogen activator (alteplase).

References

Key Words: tissue plasminogen activator
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Stroke. 2009;40:1543-1544; originally published online March 12, 2009;
doi: 10.1161/STROKEAHA.108.520676

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