Is It Ethical to Have a Placebo Arm in Reperfusion Trials in the 3- to 6-Hour Time Window?

Yes

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To date, no treatment has been proven to improve outcome when started >3 hours after the onset of acute ischemic stroke. Randomized placebo-controlled trials of new potential treatments are needed to: (1) determine if the treatment is effective; (2) determine if the treatment is effective in most patients or only in selected patients; and (3) determine, if only some patients benefit, the best way to select those whose benefit would outweighs risk.

Intravenously administered tissue plasminogen activator has not been proven effective in randomized trials beyond 3 hours. However, pooled data from these and the NINDS trial and secondary analyses certainly suggest benefit up to 4.5 to 5.0 hours. Appropriately, whether tissue plasminogen activator is effective in the 3- to 6-hour time window is presently being tested in several ongoing placebo controlled studies. The International Stroke Trial-3 trial and ECASS III will determine if the drug is effective in such patients. The DEFUSE study suggests that only patients selected by finding regions of abnormal perfusion substantially larger than areas of irreversible damage on multimodality imaging (so-called mismatch) will respond to tissue plasminogen activator between 3 and 6 hours after onset. This theory was tested in EPITHET (echoplanar imaging thrombolysis evaluation trial), which obtained MRI imaging for all patients randomized to placebo or tissue plasminogen activator in the 3- to 6-hour interval. The results showed significantly better imaging outcome and a nonsignificant trend for clinical benefit of tissue plasminogen activator in mismatch patients, but a larger placebo-controlled study is needed to confirm the observed trends. The DIAS-2 (desmoteplase in acute ischemic stroke-2) study assumed the DEFUSE data are correct and randomized only patients with either MRI or CT imaging mismatch to receive either desmoteplase or placebo between 3 and 9 hours after onset. Despite encouraging preliminary data, as yet unpublished results from DIAS-2 did not show even a trend for benefit in such patients. Therefore, the efficacy of intravenous thrombolytic treatment beyond 3 hours remains unproven and can only be answered by comparison to placebo. Even if the mismatch hypothesis is correct, it is still not known what is the critical volume of mismatch tissue to be clinically relevant, what threshold parameters should be used to determine the area of hypoperfusion, whether mismatch tissue has the same response to reperfusion regardless of the duration of hypoperfusion, and whether CT perfusion and MR perfusion are comparable.

Intra-arterial lytic therapy, endovascular clot extraction, and the like are also still of unproven effectiveness, although benefit was observed up to 6 hours in 1 phase II trial (PROACT II). Not only do these invasive methods need to be tested against placebo but also do they also need to be tested against intravenous lytic therapy. It has been convincingly demonstrated that endovascular treatment with the MERCI catheter (Concentric) can open most arteries in patients within 6 hours of ischemic stroke. It is also true that patients whose arteries are recanalized by this treatment have better outcomes than those patients in whom recanalization fails to occur in this time interval. However, mortality rate and bad outcome are substantial in these patients, and it is still uncertain that any of this “rescue therapy” is better than the best noninvasive treatment. We have found in our center that patients unselected by multimodality imaging fare no better after MERCI treatment (despite better recanalization) than do patients treated by lytics or older mechanical methods. Appropriately, the benefits of treatment with the MERCI catheter and whether patients should be selected for this treatment by multimodality imaging are presently being tested in the placebo-controlled MR RESCUE (MR and recanalization of stroke clots using embolectomy) study.

Our opinion in 2008 is that reperfusion can be effective within the 3- to 6-hour time window. This opinion is now so
widely shared among stroke experts based on the data just
described that we may well have passed the "tipping point" at
which the epidemic of treatment for these patients cannot be
halted. This would be unfortunate because the effectiveness
of such expensive and potentially dangerous treatment still
needs to be proven. Many other questions need answering as
well. What is the best way to achieve recanalization (intra-
venous tissue plasminogen activator, intravenous desmote-
plase, ultrasound, intra-venous lytics plus ultrasound, intra-venous
lytics plus antithrombotics/antiplatelets, intra-venous lytics plus
intra-arterial mechanical therapy, intra-arterial lytics alone,
intra-arterial mechanical methods alone, intra-arterial lytics
plus mechanical methods, and so on)? How do we select such
patients (MRI, CT, serological markers, clinical criteria)?
These questions can only be determined by randomized trials,
that at this point, must include a placebo arm. In the 1980s,
we also thought that patients with carotid stenosis would
benefit from carotid endarterectomy, but we were not certain
and did not know the criteria needed to select in which
patients the benefits outweighed the risks. The answers to the
carotid endarterectomy questions came from 2 well-executed
placebo-controlled trials. Similarly, the answers to therapy
for acute ischemic stroke beyond 3 hours requires the
same discipline.

So, is it “ethical” to have placebo-controlled trials given
the data? This can best be answered by posing the following
question. Would I be willing to be randomized into such a
trial at a center capable of expert intravenous or endovascular
therapy if I myself had an M1 middle cerebral artery
occlusion and NIHSS score of 15 at 4 hours after the onset of
symptoms? The answer would be a hesitant “yes,” but I
surely hope that we hurry and obtain an answer before I have
to make such a decision.

Disclosures
None.

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