Interventional Treatment of Acute Ischemic Stroke

Devices and Clinical Trials

Overview and Equipoise

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In an ideal world, our decision to enroll patients in clinical trials would be based on thoughtful, rational, informed, and balanced considerations of available and relevant scientific and clinical data. In reality, our decision making is based more often on our recent clinical experience and the opinions of those clinicians we value. To increase the appropriate and thoughtful enrollment of patients into clinical trials, it is helpful to examine how we make these decisions and the limitations of equipoise as a decision-making tool.

Physicians particularly struggle with enrollment of patients in clinical trials when a given treatment, like endovascular therapy, is already available as part of the standard of care in a region. Ideally, physicians want to offer their patients the best available medical care as opposed to treatment in a randomized trial that is selected by chance. The ethical solution to this conundrum that has gained greatest acceptance among clinicians is the concept of equipoise. According to Freedman’s classical formulation, clinical equipoise exists when there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested. Yet, Miller and Joffe note 5 considerations that argue against equipoise as the arbiter of the ethical legitimacy of randomized trials to evaluate new treatments, even for life-threatening or highly debilitating conditions (like stroke): the imprecision in defining the concept of equipoise, the reliance on expert opinion, the limitations of determining efficacy on the basis of surrogate outcomes, the high costs of new treatments, and the tendency toward premature termination of randomized clinical trials.

The expert clinical community is a highly variable group and it is unclear what the minimal proportion of this hypothetical community should be to consider that the conditions for equipoise are met (eg, 50%, 25%, 10%, or 5%). It is also very likely that the expert community of stroke interventionists may have very different ideas concerning the evidence underlying a given interventional treatment than stroke neurologists or emergency physicians who are not interventionists and whose clinical practice is not dependent on performing these procedures. Furthermore, however equipoise might be specified, systematic published data are often not available to define the degree of consensus within the expert community to guide decisions about commencing or designing randomized clinical trials, or published guidelines may lag several years behind the current state of clinical and scientific knowledge.

Even with such data, the fallibility of expert opinion in support of treatments based on surrogate measures or registry data, without evidence from well-designed randomized clinical trials, is well documented. Examples in the field of cerebrovascular disease include extracranial–intracranial bypass for carotid artery occlusion and intracranial stenting for intracranial stenosis that were no more effective than aggressive medical therapies in controlled randomized trials.

Finally, experts are subject to the same lack of relevant data and rational decision making that face the individual clinician—possibly even magnified when considered as a group. The best expert reference groups are those who publish carefully researched and evidence-based national guidelines by organizations, such as the American Heart Association. Even within these guidelines, the limitations of experts are present, particularly in those guidelines without level A and class I evidence. Moreover, the lack of equipoise by clinicians has delayed the recruitment of patients for many stroke trials, despite the lack of scientifically compelling data of the superiority of a given therapy with regards to clinical outcome. Thus, operationally, equipoise fails as a stand-alone guide of whether to enroll patients in clinical trials and has hampered the scientific community’s ability to find the best treatments for stroke patients.

The recently published book, Thinking, Fast and Slow, by Daniel Kahneman, discusses his work in behavioral economics for which he received the Nobel prize. In it, he demonstrates how all of us, even the smartest economists in the world, are subject to the errors of fast thinking, which is fast, automatic, intuitive, mentally easy, emotionally based, highly subject to biases, and the dominant way that our brain works in daily life, as compared with slow thinking which is thoughtful, analytic, and hard. Fast thinking works pretty well for easy and straightforward decision making, such as the solution to 2+2, which most adults who have graduated from grade school automatically answer correctly. However, fast thinking is highly prone to errors with harder questions that require time and mental energy, such as the solution to $47 \times 362$. The decision to enroll someone in a clinical trial is a very hard decision, and the use of equipoise as the arbiter for enrollment in trials is, unfortunately, an example of decision making based mainly on fast thinking.
Kahneman lists several biases that affect fast thinking. Some of these include the availability of information (eg, your most recent or memorable case rather than detailed data from the most relevant randomized trial), anchoring or how initial conditions influence your decision making (eg, the decision to enroll in trial if someone is a family member versus someone you do not know), priming (eg, the practice culture in a given location), and the need to see associations as causal (the lure and limitation of surrogate measures).

To illustrate the limitations of equipoise and our decision making, 2 actual cases were presented to the experts assembled at the Princeton Conference. Please answer the questions before reading what happened to the patient and what the expert group said.

Case 1 is an 81-year-old white man with prior type II diabetes mellitus and migraine who presented with sudden onset of difficulties speaking and word finding difficulties. At the time of decision making, which is 21 minutes after symptom onset, the patient has a National Institutes of Health Stroke Scale of 2 with mild and variable language problems. His blood pressure is 158/97, and he has a normal computed tomography of head and no other contraindications to tissue-type plasminogen activator (t-PA).

Figure 1. Symptomatic intracerebral hemorrhage after t-PA for patient described in case 1. Patient subsequently died.

Figure 2. Baseline and 24-h imaging for patient described in case #2. Patient went from National Institutes of Health Stroke Scale (NIHSS) of 19 at baseline to 4 at 24 h. She had modified Rankin score of 0 at 30 days. CBV indicates cerebral blood volume; rCBF, relative cerebral blood flow; and TT, transit time (images and case courtesy of Dr Brown from Hoag Memorial Hospital Presbyterian).
had a symptomatic intracerebral hemorrhage (Figure 1), and died.

Question 2: What is the risk of symptomatic intracerebral hemorrhage in randomized trials of patients with National Institutes of Health Stroke Scale of 0 to 4 treated with IV t-PA: (1) 2%, (2) 6%, (3) 10%, (4) 14%, and (5) 18%?

Of the 96 experts, 44% chose 2% (the correct answer), 42% chose 6%, 6% chose 10%, 5% chose 14%, and 3% chose 18% (it should be noted that there were some basic scientists in the response group). These answers illustrate the limitations of equipoise based on the opinions of experts and availability bias associated with fast thinking. More experts would likely have chosen a 2% risk of symptomatic intracerebral hemorrhage if the case presented to them had done well without any evidence of intracerebral hemorrhage.

Case 2 is a 71-year-old woman, who presents with 1-hour history of left hemiparesis (National Institute of Health=19) and no contraindications to IV t-PA. She has a middle cerebral arterial occlusion on computed tomography angiography and a large area of diminished relative cerebral blood flow (Figure 2).

Question 3: Would you: (1) treat with IV t-PA alone, (2) treat with IV t-PA followed by endovascular therapy, (3) treat with endovascular therapy alone if team is ready and immediately available, (4) randomize in Interventional Management of Stroke (IMS) III–like trial—IV t-PA versus IV t-PA followed by endovascular therapy.

Of the 96 experts, 17% would treat with IV t-PA alone, 18% with IV followed by endovascular therapy, 6% with endovascular therapy alone if the team was available, and 59% would randomize in an IMS III–like trial. The patient was treated with IV t-PA followed by endovascular therapy and subsequent aspiration by the Penumbra catheter with complete recanalization and modified Rankin score of 0 at 30 days.

Question 4: What is the percentage of patients with a modified Rankin score outcome of 0 to 2 at 90 days who were treated with the Penumbra aspiration device within 8 hours of onset in the Penumbra Trial and achieved thrombolysis in myocardial infarction 2 to 3 reperfusion?

Of the 96 experts, 31% chose 30% (the correct answer), 27% chose 40%, 25% chose 50%, 13% chose 60%, and 3% chose 70%. This case demonstrates considerable disagreement among the experts regarding actual published data, availability bias (the presented case did very well), and the limitation of surrogate markers. Angiographic recanalization is a visually powerful surrogate marker that has been associated with improved functional outcome in trials of reperfusion therapies. However, Figure 3 demonstrates that the relationship between recanalization and a good clinical outcome, as measured by the modified Rankin score, is dependent upon the time from stroke onset to recanalization. In reality, recanalization, by itself, is insufficient to demonstrate the superiority of endovascular therapy as compared with IV therapy or no other therapy beyond the t-PA window of 4.5 hours.

Thus, using clinical equipoise to decide whether to enroll a patient in a clinical trial is usually not based on thoughtful analytic decision making but a confluence of clinical experience and often ill-defined, and possibly incorrect, expert opinion. Even if clinical equipoise is not used as the arbiter, the decision of whether to enroll a patient in an acute stroke...
trial is often more intuitive, emotional, and experiential than rational and data-based and is chock-full of biases. For many physicians, the decision to enroll subjects in trials often reflects fast than slow thinking and thus is more prone to errors. Accordingly, we need to rely more on actual data than recent clinical experience, intuition, and the expert community. Carefully done and well-researched guidelines based on level 1 evidence are probably the best we can do regarding the expert community as a basis for equipoise. However, in the absence of prior compelling data from randomized clinical trials, patients should be randomized into well-designed clinical trials when they are available. Lack of clinical equipoise based on expert opinion and personal experience is an inadequate argument for not randomizing.

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References

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