The ISAT and ISUIA Trials

What is the impact on informed consent?

BY KIERAN P. MURPHY, MD

The International Subarachnoid Aneurysm Trial (ISAT)[1] and the International Study of Unruptured Intracranial Aneurysms (ISUIA)[2,3] are two landmark studies of intracranial aneurysm therapy. Neither is perfect, but both are changing how we manage aneurysmal disease. The trials cast doubt on well-developed medical practices and challenge the livelihood of leaders of medical communities all over the world. Naturally, these trials were interpreted differently by the coiling, clipping, and watchful waiting groups depending on how their "team" did. So, where is the signal in the noise?

ISAT

ISAT was a multicenter, randomized trial that compared the safety and efficacy of endovascular coil treatment versus surgical clipping for the treatment of ruptured brain aneurysms. To be eligible for enrollment in the ISAT trial, each patient had to be deemed equally suitable for either coiling or clipping. The investigators used the term *clinical equipoise* to describe this balance. The treatment was performed an average of 1.7 days after aneurysm rupture. Two thousand one hundred forty-three patients were randomized in 43 centers worldwide. One thousand seventy-nine patients underwent coiling, and 1,073 underwent clipping. The primary goal of the ISAT was to determine which procedure had better patient outcomes as defined by Rankin scores. The Medical Research Counsel ended the study early because the 1-year posttreatment scores showed 31% of the surgical patients were disabled or died compared to 24% of patients treated with coils. There was a 22.3% overall improvement in patients treated with coils.

> "The results of ISUIA and ISAT show that when the anatomy is favorable, an endovascular approach seems to be the treatment of choice. . ."

The European response to ISAT differed from that in the US. Our European colleagues accepted the results as recognition of technological progress and confirmation of established European medical practice. Approximately 60% to 70% of all ruptured intracranial aneurysms are treated by coiling in Europe. Conversely, in the US, the study was attacked by neurosurgeons as being fundamentally flawed. Many arguments were put forth. It was said that neurosurgeons in the US were more skillful than their European counterparts and more experienced in dealing with ruptured aneurysms. We at Johns Hopkins were the only US site in the study, and although we randomized very few patients, we are very proud of our membership of this study.

We entered the study because the relationship we had as a group of neurovascular specialists in interventional neuroradiology, neurosurgery, and neurology was strong enough to let us randomize. Such randomization fundamentally requires honesty about one's own technical weakness and is not possible in combative politicized environments. Neither participation in nor the results of this study represented a change in our daily practice. It has always been our standard practice to obtain informed consent by offering both options when they are available or, if not, to explain the benefit of one over the other

when equipoise does not exist. We have always documented these conversations in the permanent medical record.

THE ISUIA TRIAL

There have been two ISUIA studies. The first was reported in 1998 and was very controversial and widely attacked. It reported a 0.05% yearly rupture rate for intracranial aneurysms. The results were clearly affected by the inclusion of giant–skull-base aneurysms in elderly women, as these aneurysms have a very low rupture rate.[3] The more recently reported ISUIA article, published in *The Lancet* in July 2003 is a more significant work and represents a softening of the investigators' previous position. In this second study, unruptured aneurysms were randomized to coiling versus clipping, or observation. Once again, among the aneurysms randomized in the treatment arm, an endovascular approach had a 22% relative risk reduction over conventional surgery, reinforcing the results of ISAT.

> "Despite the many criticisms leveled at the ISUIA prospective data, we must reflect on its implications."

In the second ISUIA study, patients with aneurysms of the anterior circulation (defined as middle cerebral artery [MCA] or anterior communicating artery) had better outcomes when they were clipped rather then coiled. A weakness of that ISAT study was that very few of these aneurysms were randomized. This lack of randomization is consistent with our practice, in which during the past 8 years we have very rarely treated MCA aneurysms. We have found it difficult to control coil position in these clippable aneurysms. In the hands of our five neurovascular surgeons, clips can be placed to remodel an MCA aneurysm, allowing all branches to be kept open in a way that would be impossible by coiling. The use of multiple Neuroform stents (Boston Scientific Corporation/Target, Fremont, CA) is being popularized for these lesions, but the published stroke rate exceeds the surgical complication rate, so we do not do this in our practice.

Despite the many criticisms leveled at the ISUIA prospective data, we must reflect on its implications. The authors conclude that patients with no history of subarachnoid hemorrhage and an asymptomatic anterior circulation aneurysm <7 mm do not require treatment on a simple analysis of risk/benefit ratio alone. For other sizes or sites, ISUIA provides robust information for rupture risk analysis. If treatment is indicated on an individual risk/benefit analysis, which treatment should be provided? The ISUIA study failed to resolve one of the fundamental clinical problems, which is the discrepancy between their reported extremely low rupture risk in asymptomatic aneurysms <7 mm at 0.7% per year compared to the large proportion of ruptured aneurysms in this same category.

In our practice, we see an average of 172 to 180 aneurysms a year and, as in ISAT, 61% of aneurysms that ruptured are 5 mm or less. The ISUIA rupture risk is higher for larger aneurysms. How can this be reconciled with the ISUIA position that these lesions, the very ones we see most often, have the lowest rupture rate? The ISUIA investigators (led by neurologists who have focused on this area for many years) state posterior circulation aneurysms (which by definition includes aneurysms of the posterior communicating artery and the vertebral basilar system) have a higher rupture rate and appear to be more appropriate for coiling than for clipping. Patients with a history of subarachnoid hemorrhage have a higher risk of bleeding from any intracranial aneurysm.

LESSONS LEARNED

Overall, the results of ISUIA and ISAT show that when the anatomy is favorable, an endovascular approach seems to be the treatment of choice in patients older than 50 years of age and in those with posterior circulation aneurysms. For patients aged younger than 50 years with anterior circulation aneurysms, the situation is not so clear. However, in those patients, treatment options and relative benefits and risks, including postcraniotomy epilepsy, must be discussed carefully with the patient and relatives before informed consent can be obtained and elective treatment performed.

On a daily basis, we struggle with the balance of rupture risk per year versus patient life expectancy. If the patient is older than 70 years of age, we counsel the patient about risks and benefits. In our series, the risk of death from an endovascular approach in an unruptured aneurysm is well less than 1%, but the risk of stroke is approximately 5%. The risk of death in an endovascular approach to a ruptured aneurysm is approximately 5%. The risk of stroke is also 5%, and any attempt of thrombolysis in this setting is usually fatal.

We believe that there are three types of intracranial aneurysms: those that should be coiled (posterior circulation), those that should be clipped (middle cerebral, and some if not most anterior communicating artery aneurysms), and a third group that can be treated in

(Continued on page 61)