Editorial

International Subarachnoid Aneurysm Trial analysis

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The article in this issue of the Journal of Neurosurgery by Mitchell et al., who are the authors of the International Subarachnoid Aneurysm Trial (ISAT) study, is an outstanding contribution. I am particularly impressed by the objectivity of these investigators in carefully analyzing the follow-up data from the ongoing study of the initially randomized patients to question whether under some circumstances (age in this particular instance) their initial general conclusion—which essentially was that for the group of patients randomized, coil embolization was better than clip ligation—may not apply. The rationale for undertaking this carefully performed study was based on the observed differences in the postprocedural rebleeding rate, which was higher after coil occlusion, and the effect of age on this rate in patients in whom the differences in outcome between those undergoing coil embolization and those receiving clip occlusion decreased with decreasing age.

Basically, the question asked was whether in patients younger than a certain age, clip placement may be favored over coil insertion. The authors’ conclusion is that yes, it is probable that in patients younger than 40 years of age, clip ligation would be likely to result in a better long-term outcome than coil occlusion in patients with similar characteristics to the individuals randomized in the study. Needless to say, this is a very important conclusion.

The initial results of the ISAT study have been critically reviewed and carefully analyzed in a number of editorials, including our own. More than actual criticism, the bulk of these comments concerned the limited applicability of the results of the study, which should not necessarily be generalized beyond the specific subgroup of patients with intracranial aneurysms who were randomized in the trial; namely, patients with ruptured aneurysms who were classified in a relatively good neurological grade at the time of randomization and who had primarily small anterior circulation aneurysms located mostly in the anterior cerebral and internal carotid artery regions. Very importantly, only those patients in whom the treating physicians believed that the aneurysm could be treated with either procedure and could not be sure which would be better in that particular case were eligible for randomization. This resulted in only 2143 randomized patients from an initial cohort of 9559 patients who were assessed for eligibility. Indeed, most of the criticisms of the original study were directed not at the study or its authors, but rather at the interpretation of the study by the lay press, which extrapolated the results essentially to all patients with aneurysms and reached the conclusion that coil embolization was better than clip occlusion for intracranial aneurysms. The authors themselves are very careful to point out that the limitations of the original study obviously apply to this present analysis and that the results should not be extrapolated beyond the group of patients addressed in the initial study.

I am particularly impressed with the thoughtfulness of the authors’ sensitivity analysis. Because the number of rebleeding episodes was very small in both arms of the study (7 of those randomized to coil embolization and 2 of those randomized to surgery), it is obvious that just a few more or less rebleeding episodes in either arm could change the results dramatically. The authors also discuss the fact that increased longevity, which in fact has been found to increase throughout the world consistently, would favor clip placement, provided that the differences in the rebleeding rate between coil embolization and clip occlusion hold throughout the years.

Of note is the fact that the authors used, in consistency with their initial analysis, the “intention to treat” methodology. They candidly point out that of the 2 rebleeding episodes that occurred after clip ligation, 1 actually was in a coil-treated rather than a clip-occluded aneurysm, even though that patient had been randomized to the clip treatment arm. I think most sophisticated readers would agree that in fact the authors were correct from the statistical point of view to use the intention to treat analysis; however, the intuitively more rational “treatment received” type of analysis would in fact have produced a much more favorable result for clip ligation, raising the age below which clip treatment would be favored.

Concerning the sensitivity of these results, it may be useful to speculate on the potential impact of other variables on the choice of clip as opposed to coil treatment. The effect of improvements in technology is, in my opinion, likely to favor coil embolization. As much as those of us who perform only open microsurgery hate to admit, we have reached close to the zenith for open microsurgery and it is unlikely that technical improvements, which of course do
and will continue to occur, will have more than minimal impact on open surgical results. It would take a fool to deny that the younger endovascular field has a much higher potential for improvements in technology to improve results significantly and make it possible to treat aneurysms safely that cannot be treated well with current endovascular technology.

The investigators in the ISAT study are conducting careful late neuropsychological assessments of a subgroup of the randomized patients. We look forward to those results, which may or may not show significant differences in the particular cohort of patients randomized in these studies, because they were mostly good-grade patients. Nevertheless, I suspect that every neurosurgeon who operates early on patients classified in higher grades after subarachnoid hemorrhage (SAH) and who has had to fight with the “red, swollen, angry brain” wonders about the subtle effects of open surgery on the long-term neuropsychological outcome in these patients. It is my opinion that careful neuropsychological assessment will favor coil embolization over clip ligation in the higher-grade patients (Hunt and Hess Grades III and IV). Whether the results of such studies would include a detectable difference in outcome in low-grade patients who undergo clip placement rather than coil occlusion may be answered in future publications from the ISAT investigators.

In the present analysis, the authors concerned themselves only with rebleeding. What about continuing growth of those aneurysms that are not completely occluded initially either by coil insertion or clip placement? Clearly, it must be very rare for such growth to result in significant neurological decline and clip occlusion; however, in the overall picture, my suspicion is that every neurosurgeon who operates early on patients classified in higher grades after subarachnoid hemorrhage (SAH) and who has had to fight with the “red, swollen, angry brain” wonders about the subtle effects of open surgery on the long-term neuropsychological outcome in these patients. It is my opinion that careful neuropsychological assessment will favor coil embolization over clip ligation in the higher-grade patients (Hunt and Hess Grades III and IV). Whether the results of such studies would include a detectable difference in outcome in low-grade patients who undergo clip placement rather than coil occlusion may be answered in future publications from the ISAT investigators.

Another factor for which eventually the authors of the ISAT study may have some data to share with us is cost. Cost is currently an important issue in much of the developing world, where patients may have to pay for their own coils and endovascular equipment, or where such items simply cannot be afforded by the socioeconomic circumstances of the country. My suspicion is that the developed world will not remain immune to cost considerations and that some form of rationalization of care is likely to take place. This trend may favor coil occlusion, if indeed this treatment is found to be less expensive than coil embolization, as I suspect it will.

What about the effect of increased regionalization? It is hard to escape the conclusion that this will take place in the future, considering the plethora of studies that have suggested better results at large-volume centers and by large-volume surgeons. It would not be difficult to predict that such trend will lead to better results for both coil embolization and clip occlusion; however, in the overall picture, my belief is that surgical results will improve more in relation to endovascular results. I say this because, at least in the US, currently only ~ 25% of clip ligation procedures for aneurysms take place at major regional centers, where results have been proven to be superior. In contrast, endovascular treatment is already likely to be more regionalized than open neurosurgery because there are currently fewer trained endovascular surgeons than neurosurgeons capable of doing a craniotomy. It is also likely that, under equal circumstances, results of coil embolization will deteriorate as more and more specialists, not only from neuroradiology and neurosurgery, but also from neurology and possibly even cardiology, move into this lucrative field.

Finally, I would like to speculate on the choice of clip as opposed to coil treatment in the large categories of patients that were not addressed by the ISAT study. Unruptured aneurysms are of course a very important and growing group, given the improvements in and greater availability of non-invasive testing. Although the practice varies throughout the world, I suspect that at least in the US, the bias nowadays is in favor of clip ligation for unruptured aneurysms, given the fact that with these patients we are more concerned with the long-term efficacy of the procedure, which is known to be very good for microsurgery and is relatively less known but probably worse for coil embolization. My prediction is that for a variety of reasons—including improvements in technology, greater availability of well-trained endovascular surgeons, patterns of referral, and so on—a greater proportion of unruptured aneurysms will be treated endovascularly in the future. High-grade patients were not adequately addressed by the ISAT study, in which 88% of the patients were classified in Grades I and II. It is in the higher-grade patients that I think neuropsychological studies will eventually demonstrate the advantages of coil embolization over clip ligation. Although high-grade patients with a “red, swollen, angry brain” ordinarily wake up from surgery and are able to walk and talk by the time of discharge, I find it hard to believe that having manipulated and retracted such a brain does not result in at least a subtle degree of neuropsychological deterioration above and beyond the effect of SAH per se; such manipulations of the brain, of course, are not necessary with endovascular surgery.

Posterior circulation aneurysms were also not addressed by the initial study, because they constituted only 2.7% of the total number of patients enrolled. Within this group, every experienced neurosurgeon knows that there are some lesions that are not very different from anterior circulation aneurysms in terms of the need for surgical retraction and depth of exposure. Such is the case with vertebral and posterior inferior cerebellar artery aneurysms, in which the surgical results are similar to those for anterior circulating aneurysms. Such may also be the case with most superior cerebellar artery aneurysms that are, of course, not associated with perforating vessels, which is the main problem with open surgery for basilar tip aneurysms. At least for most basilar tip and basilar trunk aneurysms, it is my opinion that endovascular therapy is currently preferable and is likely to remain so in the future. Middle cerebral artery aneurysms were underrepresented in the initial ISAT study. At least in this country, most of these aneurysms are currently treated by clip occlusion, given the relative ease of accessibility with surgery and the greater difficulties associated with endovascular navigation to this site. It is my opinion, however, that the current advantage of open neurosurgery for middle cerebral artery aneurysms will fade with better technology for endovascular navigation and coil insertion.

Large and giant aneurysms were also markedly ununder-