Barrow Ruptured Aneurysm Trial


BRAT was a response to the International Subarachnoid Aneurysm Trial (ISAT). McDougall et al. wrote:

A major criticism of ISAT has been that a large number of patients treated at trial centers during the study were not included in the trial... Implicit in determining eligibility for ISAT was… consensus that either technique would be a suitable treatment option; and consensus that it was uncertain whether the ruptured aneurysm should be treated by neurosurgical or endovascular means. As a result of this policy, more than 9559 aneurysms were screened, but only 2143 patients were enrolled.

It is crucial to expose what was done to patients in BRAT in an attempt to address this weakness of ISAT:

... patients were assigned to a surgeon with a prestated treatment intent (coil or clip), but before embarking on that intended treatment, the assigned surgeon would naturally, as in daily practice, make a treatment decision based on what that practitioner believed would provide the best outcome for that particular patient. This decision may be to proceed with the “intended” or assigned treatment, or it may be that surgeon’s judgment that a particular patient would be better served by the other treatment modality, in which case the patient would “cross over” to the alternative treatment.

Because 205 (98%) of 209 treated patients assigned to surgical clipping underwent coil placement, but only 124 (62%) of 199 treated patients assigned to coil embolization underwent coil treatment (the other 75 were treated by means of clip placement), we can safely surmise that the real, overall treatment philosophy of the Barrow Neurological Institute was: clipping is the “standard,” default treatment; coiling may be a good option, but only in selected cases. Coil embolization was offered to 124 (30.4%) of 408 treated patients, 17% of all 725 screened patients. This is hardly better than ISAT.

If the authors thought that imposing this process on patients served to improve the scientific credibility of their results, they were wrong. How can a group cherry-picked to include only those cases most favorable to coil embolization be fairly compared to a clip occlusion group that included everybody? (or everybody plus patients rejected from coiling?) We have in fact replaced the problem of eligibility in ISAT (what would results be had all patients been included?) with a new problem (what would have happened if patients had not been so stringently selected?). What would have happened if the surgeons had turned away a group of patients with aneurysms, and the endovascular specialists treating with coil embolization could not refuse? Finally, the burning question: how did endovascular specialists judge that coil embolization would provide the best outcome for a particular patient? It is unclear what to do with BRAT results; perhaps BRAT has taught us that a policy of “right of first refusal” for coil embolization can lead to better outcomes in a selected group of patients, as compared to a policy of clipping for all patients, but we already knew that from ISAT. What about all the other patients (with non-BRAT or non-ISAT aneurysms)?

We must remember that we cannot get answers to questions we never ask. If we want to know which of 2 options offers the best chance of the best outcome for an individual patient, both options must be available to that patient. Hence there is only 1 way to make valid comparisons that can be applied to clinical decisions in individual patients: to compare results of 2 options in patients eligible for both treatment options. There can be no ethical shortcuts; we must declare patients eligible for both options before knowing the results of treatment allocation. To do that, physicians are forced to admit the uncertainty to each patient with transparency, and to present alternatives in a truly balanced fashion prior to obtaining consent.

The BRAT was not, in fact, a randomized trial, but a registry of patients treated in 1 of 2 ways: Group A is made up of patients who happened to arrive on surgical days. They are told that surgery provides the best outcome for their particular case. Group B is made up of patients who happened to arrive on endovascular days, further selected to be the best cases for coil embolization, and patients are told that this treatment is believed to provide the best outcome for their particular case.

One purpose of BRAT was “to reflect real-world practicalities of ruptured aneurysm treatment in North America.” In that respect, the authors of the study are, unfortunately, perfectly correct, since the way medical care is delivered in almost all institutions across North America, and the way research was performed in BRAT, ensures that 1) not a single patient is really told about the uncertainty—they are told the physician always knows “the best choice;” 2) not a single patient is given a 50% chance of escaping our poorly justified beliefs; and 3) patients are not really free to participate—they are easily convinced to accept the physician’s preferred treatment. These, we claim, can be considered serious breaches in medical ethics, breaches that would be prevented with proper trials. That this way of treating patients seems “natural” to the designers of BRAT only reflects the vitiating and paradoxical nature of the notion of trust in the current physician-patient relationship: better pretend we know, even when we do not, to preserve patient trust and the illusion of physician omniscience and infallibility. But
how can we expect patients to continue to trust us, when we have admitted our uncertainty to each other, to the institution, to the ethics review board, but not to them, the ones who must bear the treatment outcome? Medicine in general and neurosurgery in particular will not progress until this conception is replaced with a more mature relationship, in research and medical care, a relationship that admits uncertainties when they exist, and squarely confronts them with properly designed trials. We are still far from this revolution.

A better, more ethical way would have been to offer the new treatment to each patient, but only as a 50% chance of getting the new treatment (coil embolization), with a 50% chance of getting the conventional treatment (clip placement), and only to patients the surgeon believed had a good chance of having a better outcome with the new treatment. The important point is that the physician does not really know and must admit this to the patient. This is difficult, but possible; this is, in fact, the design of ISAT.

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References

RESPONSE: We are grateful for the opportunity to discuss our work and provide clarification where needed. Darsaut and Raymond have raised several interesting points, which are addressed below in the sequence in which they were raised.

Darsaut and Raymond “surmise” that clipping was the standard therapy and note that treating 124 patients with coil embolization in this study meant that coiling was offered to only 17% of the screened patients and that this was, therefore, “hardly better than ISAT.” The actual patient flow was clearly described in our study. To compare numerators from different parameters of the 2 studies over the common denominator of number of patients screened for their calculation is misleading. About one-fifth of patients screened for ISAT were enrolled, whereas two-thirds of patients screened for BRAT were enrolled.

As Darsaut and Raymond are well aware, no study can recruit all patients screened, and many patients screened do not meet eligibility requirements. Half of the patients in BRAT were assigned to coiling and those who did not receive coils did not receive them for the reasons stated—hematomas that required evacuation, aneurysms too small to be safely coiled, and so on. To surmise that clipping was the standard therapy is simply wrong. The standard therapy for a given patient was the therapy to which the patient was assigned during the course of the trial.

But the comparison is misplaced for a more basic reason. First, although we note that the ratio of screened to enrolled patients in ISAT was a common criticism (as referenced in our article), we did not suggest that this criticism invalidated the findings of ISAT with respect to the patient population studied or even that it was a valid criticism. It was a simple recognition that in the mind of many clinicians, the ratio of screened to enrolled patients begged the question of whether the results of ISAT were broadly generalizable to the entire population of patients with ruptured aneurysms.

We tried to address this issue with BRAT by including all patients. The study therefore predictably incorporated many patients who were not really candidates for coiling, thus creating a level of “statistical noise.” As stated, BRAT was intended as a pilot study, with a view to a more rigorous multicenter trial. Gaining insight into the level of “noise” seemed an important step in determining the viability of such a trial. We did not suggest that BRAT was a “better” trial than ISAT; the trials represent 2 ends of a spectrum.

The BRAT studied a selection process in which the standard alternated between clipping and coiling. The intention-to-treat analysis tests the decision-making process more so than the procedure and counted all patients in the assigned treatment group—not a cherry-picked group of only favorable cases. An approach to coiling that is either more or less aggressive may well produce different results. The more appropriate question is whether morbidity and mortality rates can be further lowered by more or less aggressive selection for coiling.

Likewise, this point holds as a response to Darsaut and Raymond’s question of what would have happened if the surgeons treating with clip placement “had turned away a group of patients with aneurysms, and the endovascular specialists treating with coil embolization could not refuse?” To be unable to refuse providing a particular treatment seems an unlikely hypothetical situation. Nonetheless, for the sake of argument, the answer is that a different outcome would be expected. Because of the intent-to-treat analysis, however, the result—good or bad—would have been assigned to the clipping arm. If the clipping surgeon had a patient who, for whatever reason, the surgeon believed would have a better outcome if treated with coil embolization, it would be better strategically to cross that patient over to coiling so that the presumed better outcome would be applied to the assigned (that is, clipping) group.

Their question about how decisions were made regarding particular patients is answered in the manuscript. The primary decision for coil embolization was based on the anatomical favorability of the aneurysm for endovascular treatment. In ISAT, patients with unfavorable