

Giuseppe Lanzino

Treatment of
**INTRACRANIAL
ANEURYSMS**



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Preface

Vascular neurosurgery in general, and surgery of intracranial aneurysms in particular, have always been perceived as being among the most challenging — but also most rewarding — branches of neurosurgery. Over the past few years, innovations and refinements in microneurosurgery, endovascular techniques and periprocedural adjuncts have resulted in a dramatic outcome improvement. Nowadays, treatment of intracranial aneurysms can be performed with very low morbidity and mortality rates. In order to consistently achieve the best outcomes possible, careful patient selection, individualized treatment and superb clinical and technical skills are required. This book is intended as an updated review of the current management of these challenging lesions, with an eye to decision-making, and to basic and advanced microsurgical and endovascular techniques.

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Trials and tribulations: an evidence-based approach to aneurysm treatment

T. SORENSON, G. LANZINO

With the introduction of Guglielmi detachable coils (GDCs) in 1992, endovascular treatment of aneurysms has become an increasingly valid alternative to traditional surgical clipping.¹ Several trials on ruptured aneurysms have validated endovascular treatment;² there is no definitive conclusion regarding treatment of unruptured aneurysms as there have not been head-to-head studies comparing the two modalities. In this chapter, we review these ruptured aneurysm clinical trials and discuss their results, some of the subgroup analyses, and present our current approach to patients with intracranial aneurysms.

CLINICAL STUDIES

THE KUOPIO STUDY

The first prospective randomized study to examine the efficacy of coil embolization when treating ruptured intracranial aneurysms took place as a single-center trial based at Kuopio University Hospital in Kuopio, Finland. During the trial period (February 1, 1995–August 31, 1997), any patient admitted with primary subarachnoid hemorrhage (SAH) was considered for the trial. Exclusion criteria included: patients older than 75 years, bleeding occurring more than three days prior to procedure, presence of associated hematoma requiring urgent evacuation, mass effect causing neurological deficit, or previous surgery for ruptured aneurysm. Additional aneurysm-related factors leading to exclusion from the study were aneurysm neck wider than fundus, fusiform morphology, neck relationship to parent vessel with adjacent branches not distinguishable, and diameter of aneurysm smaller than 2mm (smaller than the smallest coil available at the time of the study). Excluding any cases that fell under these conditions, 109 patients were enrolled and randomly assigned to the endovascular (52 patients) or the surgical (57 patients) treatment groups. Based on the pretreatment Hunt and Hess Scale,³ 67 patients were grade I–II, 26 patients were grade III, and 16 were grade IV–V. Ninety-eight of the ruptured aneurysms were located in the anterior circulation while 11 were located in the posterior circulation⁴.

In the Kuopio Study, one year after treatment 33% of patients in the surgery group and 23% in the endovascular group suffered a poor outcome, the difference being not statistically significant.⁵ Overall angiographic results were significantly better in the clipping group than the endovascular one, although subgroup analysis indicated that angiographic results were better in the surgery group for anterior circulation aneurysms but complete obliteration rates were better in the posterior circulation for the endovascular group.⁴ Treatment-related mortality was 4% and 2% in the surgical and endovascular cohort, respectively.

This study represented a first attempt to provide a head-to-head comparison between the two treatment modalities. It was initiated soon after introduction of detachable coils and reflected early experiences with endovascular coil embolization in a small cohort. Nevertheless, it suggested a trend toward better functional recovery after endovascular treatment at the expense of a higher rate of incompletely obliterated aneurysms. Despite the important rate of incomplete angiographic obliteration in the endovascular cohort, no rebleeding was reported beyond the acute phase⁵.

THE INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL

As endovascular coil embolization was being proposed as a possible and potentially less invasive alternative to surgical clipping, a large, multicenter study (International Subarachnoid Aneurysm Trial, ISAT) was launched mostly in the United Kingdom and Europe to answer the question about the best therapeutic strategy for patients with ruptured aneurysms. Patients with ruptured aneurysms causing SAH were randomly allocated into either surgical clipping or endovascular coiling between 1994 and 2002.⁶ Intrinsic to ISAT was the concept of “equipoise”, i.e. for a patient to be considered for enrollment the target aneurysm had to be amenable to either surgery or endovascular therapy as judged by specialists in each treatment modality. Overall, of 9559 patients screened at the participating centers, 2143 were eventually randomized. More than 90% of patients enrolled in ISAT were patients in good neurological condition, i.e. World Federation Neurosurgical Societies (WFNS) Grades I-III with small (less than 10 mm) aneurysms of the anterior circulation. The trial was prematurely halted because of a statistically significant difference between the two groups. Patients allocated to endovascular treatment experienced better functional outcome (mRS greater than 2) at one year. Rates of dependency or death were 24% and 31% in the endovascular and the surgical groups, respectively ($P=0.0019$).

Publication of the ISAT results in 2002 resulted in a major shift in the treatment of intracranial aneurysm in many centers throughout the world. However, several questions still remained unanswered. These questions pertained primarily to the durability of endovascular treatment and the general application of ISAT findings to the overall population of patients with ruptured aneurysms. The ISAT investigators also confirmed that endovascular treatment (at least as it was conducted in the years of the trial) was associated with a high incidence of incomplete angiographic obliteration leading to a relatively high percentage of retreatments.⁷ The question then arises whether the outcome advantage of endovascular treatment is overcome over the years by a higher incidence of rebleeding and morbidity/mortality related to the incomplete treatment. To answer this very important question, the ISAT investigators have published updated follow-up of the original cohort at 10 and, most recently, 18 years. In these updates, despite a slightly higher incidence of rebleeding from the target aneurysm in the endovascular cohort (cumulative risk of rebleeding 0.0216 for endovascular *versus* 0.0064 for surgical clipping), the functional outcome advantage was still maintained after many years of follow-up.⁸

The wealth of data acquired by ISAT has allowed a number of subgroup analyses of patients enrolled in the trials. While the results of most of these analyses must be interpreted with caution since many of these endpoints were not prespecified at the trial onset, these data still represent the best data available on this subset of patients. Mitchell *et al.* analyzed outcomes in relation to treatment modality for patients enrolled in ISAT with relation to age.⁹ They concluded that surgical clipping might be superior to endovascular treatment in the subset of very young (<40 years) patients. Younger patients tolerate surgery better than older ones and might benefit more

from the longer lasting protection against rebleeding afforded by surgical treatment. From other subgroup analyses of ISAT data, it was also suggested that the incidence of seizures¹⁰ and ischemic complications from vasospasm⁵ were lower in patients undergoing endovascular treatment than those undergoing surgical treatment.

Another important aspect to consider when evaluating ISAT results is that patients' outcome for the first time was actually self-assessed. In the ISAT follow-up, outcome was assessed based on patients' own interpretation of their functional status by a self-filled questionnaire. The questionnaire was filled out by a caregiver if patients were unable to self-assess their outcome because of their neurological morbidity. Therefore, unlike other trials, the outcome was not assessed by a third party, but by the patient themselves. This self-assessment is important, because it is ultimately what matters when assessing outcome.

Similarly to the International Study of Unruptured Intracranial Aneurysms (ISUIA), ISAT also demonstrated that the long-term outcome of patients with intracranial aneurysms is overwhelmingly affected by a high incidence of cardiovascular disease and cancer rather than rebleeding from the target aneurysm. These observations underscore the fact that to improve the long-term outlook of these patients, interventions aimed at smoking cessation and control for risk factors of atherosclerosis (in particular hypertension for this patient population) are of paramount importance in improving the long-term follow-up (ISUIA Investigators, Unpublished data).⁸

THE BARROW RUPTURED ANEURYSM TRIAL

As mentioned above, one of the main criticisms of ISAT was the potential lack of generalizability of the trial's results given that only a minority of the patients screened at the participating centers eventually were eventually enrolled in the trial. Moreover, there were concerns that the trial's results might not be applicable to countries like the United States, as surgeons in the United States could have had a higher degree of sub-specialization than those practicing elsewhere. To address this and other potential shortcomings, the Barrow Ruptured Aneurysm Trial (BRAT) Study was initiated at the Barrow Neurological Institute in Phoenix, AZ, USA where operators with a high degree of sub-specialization and skill performed surgical or the endovascular procedures.

In order to remove any potential preselection of patients, the BRAT investigators enrolled every patient to consent to the study irrespective of the neurological grade, location and or geometry of the aneurysm. While this selection criteria allowed for the vast majority of patients with ruptured aneurysms and SAH to be enrolled in the trial, it also resulted in a number of challenges. The enrollment criteria resulted in a large number of patients with no aneurysm or SAH being enrolled in the study and a high rate of crossover between modalities, particularly from endovascular to surgical clipping as many aneurysms not ideal for endovascular treatment were randomly assigned to coiling. Unfortunately, these factors have clouded interpretation of the results.

Despite these limitations, the BRAT study confirmed what the Kuopio and the ISAT had previously shown. In patients with ruptured aneurysms, endovascular treatment was associated with a lower rate of poor outcome at one year (Table I).² This was present both in the intention to treat and as treated analyses.¹¹ Three and six year updates of the BRAT study also showed that the difference between the two methods lessens in importance over time.^{12, 13} Endovascular treatment is associated with a statistically significant better outcome in patients with posterior circulation intracranial aneurysms both at short and long-term follow-up.

SUMMARY OF RANDOMIZED TRIALS FOR RUPTURED ANEURYSMS

Publication of the aforementioned trials has sparked a heated debate over the best treatment modality for patients with intracranial aneurysms. Unfortunately, the arguments brought forward in this debate are not always moved by pure scientific interest. There is no question that each of the trials mentioned has important limitations as it pertains to any trial assessing an invasive procedure. However, we feel that from an objective analysis of the data some conclusions can be made.

Endovascular coil embolization is associated with a better functional outcome and quicker recovery in patients with ruptured aneurysms and SAH. Therefore, it should be considered as the primary treatment modality for patients with aneurysms that are suitable to coil embolization. However, patients undergoing endovascular therapy require close radiological follow-up because of the risk of aneurysm recurrence and subsequent need for retreatment. Thus, endovascular treatment might not be the best option for non-compliant patients who might not return for follow-up imaging studies.

Aneurysms in locations such as the middle cerebral artery and very small aneurysms, which can be challenging from endovascular point of view, might benefit from surgical treatment, as this treatment might still be associated with lower incidence of major complications. Most importantly, a careful and objective individualized assessment to one treatment modality over another in single patients is the best modality for excellent outcomes. With improvement in surgical and endovascular techniques, complications tend to be associated less and less with technical factors and mistakes and more often are the result of poor judgment in the choice of one technique over the other.

In our current practice, approximately 65-70% of patients with ruptured aneurysms undergo endovascular treatment while the remaining patients are considered for surgical treatment. The availability of two complimentary therapeutic modalities and improvements in neurocritical care has increased the likelihood of complete neurological recovery in patients with SAH. Because of these improvements in our unit, we expect every patients with WFNS grade I-IV aneurysmal SAH without associated intraparenchymal hematoma, who have had a witnessed event and who improve after CSF diversion, to return to their pre-SAH level of functioning in 3-6 months.¹⁴

There are currently no completed trials looking specifically at endovascular versus surgical

Table I - Summary of results from clinical studies observing endovascular versus surgical treatment for ruptured aneurysms.

	Kuopio	ISAT	BRAT
Follow-up assessment	Single neurosurgeon	Self-assessed via postal questionnaire	Third party research nurse
Poor outcome definition	GOS	mRS >3	mRS >3
Endovascular poor outcome	23% (12/52)	23.5% (250/1063)	23% (46/198)
Surgical poor outcome	33% (19/57)	30.9% (326/1055)	34% (69/205)
Endovascular death	13% (7/52)	8.0% (85/1063)	N/A
Surgical death	16% (9/57)	9.9% (105/1055)	N/A
Endovascular rebleeding	0.9% (1/109)	1.7% (36/2143)	0.2% (1/471)
Surgical rebleeding	0%	0.6% (13/2143)	0.2% (1/471)
Endovascular one-year follow-up	100%	99% (1063/1073)	85% (198/233)
Surgical one-year follow-up	100%	98.6% (1055/1070)	86% (205/238)

Adaptation of Table II from Lanzino *et al.*²

treatment of unruptured aneurysms, though such a trial is ongoing. The Canadian Unruptured Endovascular Versus Surgery (CURES) trial began in 2010 and is estimated to finish by 2025. The purpose of the trial is to determine the efficacy of endovascular coiling as compared to surgical clipping for treating unruptured intracranial aneurysms and is evaluating a number of end-points. These include treatment success or failure, overall morbidity and mortality, occurrence of morbidity and mortality post-treatment, peri-treatment hospitalization lasting more than five days, discharge following treatment to a location other than home. Eligibility for the CURES trial is defined by: patient age >18 with at least 10 years of remaining life, at least one documented intradural saccular intracranial aneurysm, aneurysm size between 3 and 25 mm, and patient and aneurysms considered appropriate for either treatment technique. Exclusion criteria include: any previous intracranial hemorrhage, baseline mRS>2, single cavernous, dissecting, fusiform, mycotic, or AVM associated aneurysms, and pregnancy, among others. This trial is taking place across five Canadian and one Belgian hospital centers. This study is currently recruiting patients.¹⁵

CONCLUSIONS

Several trials, each with its own methodological flaws, have compared endovascular coil embolization to surgical clipping for ruptured intracranial aneurysms. Overall, these trials have shown that endovascular coil occlusion is associated with better functional outcomes at one year at the expenses of higher rates of incomplete aneurysm exclusion, exposing the patient to higher rates of retreatment. The aforementioned trials were completed several years ago and endovascular techniques have only improved since then. Currently, the widespread availability of three-dimensional angiography and improved microcatheter and coil technology have resulted in better outcomes and have enlarged the potential pool of patients amenable to endovascular techniques. Despite this remarkable progress in the treatment of aneurysms, endovascular techniques still have some limitations and there are several situations in which surgical clipping is a better choice. With more than one technique available for patients with ruptured and unruptured intracranial aneurysms, an individualized approach that takes into account various patient and aneurysm-related factors is key to obtaining superior outcomes.

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