Review Article

Clipping versus coiling for ruptured intracranial aneurysms after the international subarachnoid aneurysm trial

United Kingdom experience

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ABSTRACT

صممت الدارسة العالمية للنزف تحت العنكبوتية الناجم عن تمزق أمهات الدم الدماغية، كأول دراسة دولية تعتمد على أسس إحصائية لدراسة الفرق في السلامة والفعالية بين طريقتي العلاج المعتمدة لحالات تمزق أمهات الدم الدماغية: العلاج الجراحي والعلاج بالقسطرة، وقد نشرت النتائج الأولية لهذه الدراسة في مجلة اللانسيت عام 2002م، ظهر فيها وبكل وضوح تفوق العلاج بالقسطرة على العلاج الجراحي، حيث أن 22.7% من المرضي الذين عولجوا بالقسطرة أصبحوا معاقين إعاقة شديدة أو في عداد الأموات، مقابل 30.6% في المجموعة الجراحية مع انخفاض خطورة مطلق بقيمة 6.9%. أثارت نتائج الـ (ISAT) ضجة كبيرة في الأوساط الطبية ووسائل الإعلام، وعلى الرغم من الانتقادات لهذه الدراسة فإن نتائجها قد أحدثت تأثير كبير على علاج أمهات الدم الدماغية المتمزقة (SAH) خاصة في المملكة المتحدة. كما أصدرت مجموعة الباحثين (ISAT) الذين قاموا بهذه الدراسة نتائج أخرى لاحقة حول مواضيع أخرى متعلقة بالدراسة مثل خطورة عودة النزف بعد العلاج أو تكرار العلاجات أو خطورة الإصابة بالصرع إضافة إلى التكلفة العلاجية لطريقتي العلاج المعتمدة.

The International Subarachnoid Aneurysm Trial (ISAT) was designed as the first multi-central international prospective randomized trial aiming to compare the safety and efficacy of the 2 available treatments for ruptured intracranial aneurysms; endovascular coiling and surgical clipping. The initial results were published in the Lancet (2002), and it showed clearly a superiority of coiling over clipping in the treatment of ruptured intracranial aneurysms; 22.7% of coiled patients were dependent or dead compared with 30.6% in the surgical group with absolute risk reduction of 6.9%. The results of the ISAT drew huge attention from both scientific authorities and lay media. Despite criticisms, the study has made a significant impact on the treatment of aneurysmal subarachnoid hemorrhage, especially in the United Kingdom and Europe. Since their initial results, the ISAT group has published further papers and updates covering more interesting results regarding the risks of rebleeding, repeat procedures, epilepsy, and the cost effectiveness of both treatments.

Neurosciences 2009; Vol. 14 (2): 118-123

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Rupture of an intracranial aneurysm is the most common cause for subarachnoid hemorrhage (SAH). It represents less than 5% of all strokes with an incidence of 6-10 per 100,000 population in most western countries.[1,2] Aneurysmal SAH is a serious disease, the risk of rebleeding from the ruptured aneurysm is around 50% in the first 6 months from the ictus. Other risks including vasospasm, hydrocephalus, respiratory failure, cardiac dysfunction, and electrolytes imbalance make the disease serious and carries a high chance of mortality and morbidity. Following the discovery of cerebral angiography by Moniz in 1927,[3] surgeons tried different methods to obliterate the aneurysm and prevent further bleeding. Dandy in 1937,[4] was the first to perform surgical clipping of intracranial aneurysm using a metal clip. In the 1960s, McKissock and colleagues[5-7] published a series of prospective randomized trials that showed the benefits of surgical clipping of intracranial aneurysms. The risk of surgery has declined dramatically in the last 30 years following the advances in microsurgical techniques, anesthesia, intensive care, and radiological imaging. Despite all these major advances, the prognosis remains poor with an overall mortality of 30% or more, and less than 50% of patients making a full functional recovery.[8,9] In

1991, Guglielmi and his colleagues,[10] published their preliminary clinical experience on a new detachable platinum coil device (GDC), which can be inserted into the aneurysm sac via the endovascular route and causes electrothrombosis. This new method has proven effective in preventing early rebleeding from ruptured intracranial aneurysm.[11] However, the total obliteration rate of the aneurysms seems lower than that achieved by clipping.[12,13] Since the approval of this new device by the US Food and Drug Administration in 1995, endovascular coiling has become widely used in patients with ruptured and unruptured intracranial aneurysms.[13] The introduction of this new alternative method for treating intracranial aneurysms raised the question of how and when endovascular treatment should be used. There was also a need for randomized prospective studies to establish the efficacy and safety of GDC compared to surgical clipping.[14] Until 2002, there was only one small prospective randomized trial of 109 patients with ruptured intracranial aneurysm treated in a single center. The results of this study showed no difference in the clinical and neuropsychological outcomes of both treatment modalities at one year.[15]

What is ISAT? The International Subarachnoid Aneurysm Trial (ISAT) was designed as the first multi-central international prospective randomized trial aiming to compare the safety and efficacy of the 2 available treatments for ruptured intracranial aneurysms; endovascular coiling, and surgical clipping. Between 1994 and 2002, a total of 2143 patients with aneurysmal SAH were randomly assigned to either clipping (1070) or coiling (1073) in 42 neurosurgical centers, mainly in the United Kingdom (UK) and Europe (**Table 1**). The primary outcome was death or dependence at one year as defined by a modified Rankin scale of 3-6. Other secondary outcomes included the risk of re-bleeding and the risk of epilepsy. In the initial analysis of one year follow up for 1594 patients (out of 2143) the difference in outcome was significant enough for the study to be stopped in May 2002. The results were published in the Lancet in October 2002.[14] The study showed a superiority of coiling over clipping in the treatment of ruptured intracranial aneurysms; 22.7% of coiled patients were dependent or dead compared with 30.6% in the surgical group, with absolute risk reduction of 6.9%. However, the risk of re-bleeding from treated aneurysms and the risk of repeat procedures was higher in the coiling group.

Limitations of ISAT. The results of the ISAT drew huge attention from both the scientific authorities and the lay media.[16] A number of criticisms, mainly from neurosurgeons of the study and its results have been made both in Europe and the United States (USA).[17-20] Two neurosurgical societies have also released "Position Statements" criticizing the results of ISAT,[21,22] whereas it has received support from neuroradiological societies.[23] The 3 main limitations of the ISAT can be summarized as follows; The first point is with the selection process; out of the 9559 patients enrolled for the study, only 2143 (22.4%) were actually randomized. The contribution of the participant centers to the study varied between 1-44% of their real patient population. Of the patients, 88% had a good clinical grade (WFNS grade 1 and 2), and the aneurysm size was less than 10 mm in 92% of the cases. In addition, 97% were anterior circulation aneurysms. These facts indicate a selection bias and would make the results of the study applicable mainly for good grade, small, anterior circulation aneurysms. In addition, the above selection of aneurysms is considered as good predictors for favorable surgical outcome. However, surgical outcomes in the ISAT study were criticized as being slightly worse compared to other studies (**Table 2**).[24] The second main point is the differences in care between the different recruited centers and the experience of their neurosurgeons and neuroradiologists. Many experts believe that most of the coiling in the ISAT was performed by experienced neuroradiologists, while most of the clipping was performed by general neurosurgeons or even trainees. This fact reflects the common practise in treating

Table 1 - Distribution of the recruited patients in the International Subarachnoid Aneurysm Trial according to participating countries.[24]

Participating country	Patients recruited n (%)	
United Kingdom	1644	(76.7)
Sweden	123	(5.7)
Germany	118	(5.5)
Canada	89	(4.2)
Finland	63	(2.9)
France	43	(2.0)
Australia	27	(1.3)
Denmark	25	(1.2)
Others*	11	(0.5)

*Switzerland, USA, and Czech Republic

Table 2 - Comparison of surgical outcomes and patient populations of the International Subarachnoid Aneurysm Trial and other large series.[24]

Study (no. of patients)	Favorable outcome	Good pre-op grade	Anterior circulation	Small size aneurysms
ISAT (n=1070)[14]	69%	88%	97%	93%
Kassell et al (n=2922)[38]	78%	89%	92%	79%
Osawa et al (n=2055)[39]	69%	79%	94%	93%

Table 3 - The outcomes of the International Subarachnoid Aneurysm Trial (2002).[14]

Outcomes	Surgical clipping	Endovascular coiling
	% of patients	
Dependant or dead (one year)	30.6	23.7
Repeat procedures	3.2	12.7
Post-procedural re-bleed (one year)	1.3	3.2

Table 4 - The outcomes of the International Subarachnoid Aneurysm Trial (2005).[29]

Outcomes	Surgical clipping	Endovascular coiling
	% of patients	
Dependent or dead (one year)	30.9	23.5
Incidence of seizures (from discharge)	6.35	3.8
Complete occlusion of target aneurysm	82.0	66.0
Re-bleed (after one year)	0.2	0.65

Table 5 - Number of retreatment cases in the coiling and clipping arms of the International Subarachnoid Aneurysm Trial (ISAT) study.[30]

Retreatment	Coiling group (n=1096)*	Clipping group (n=1012)*
Early (1-3 months)	97 (8.8)	30 (2.9)
Late (>3months)	94 (8.6)	9 (0.9)
Regrowth	34 (3.1)	9 (0.9)
Residual filling	60 (5.5)	0 (0)

*Number of patients who were treated by primary coiling or clipping from the original ISAT cohort

ruptured intracranial aneurysms in UK centers before the ISAT.[19,20] The third point is the long-term efficacy of coiling in preventing late rebleeding. In the follow up angiographic studies of the ISAT patients, complete occlusion of the aneurysm was achieved in 66% of the patients in the coiling group compared with 82% of the surgical group. Retreatment (repeat procedure) was performed in 12.7% of the patients in the coiling group, compared with 3.2% in the surgical group. Furthermore, the one-year risk of re-bleeding was 3.2% in the coiling group and 1.3% in the surgical group (**Table 3**). All these results raise questions on the long-term efficacy of coiling and the duration of follow up needed by the study to assess the safety of coiling, especially in younger patients.[24] The study however, was well conducted and uncertainties revolve not around its reliability, but around its extrapolation to patients in different clinical situations at different historical time periods.

Impact of ISAT. Despite the criticisms it was clear, especially in the UK, that coiling of ruptured intracranial aneurysms has increased after the ISAT. In a single large neurosurgical unit (Hope Hospital, Manchester, UK) the number of patients undergoing surgery has decreased from 51% (pre-ISAT) to 31% (post-ISAT), while endovascular treatment of aneurysms increased from 35-68%. Simultaneously there was a non-significant trend toward better Glasgow outcome scores at 6 months follow up. The length of stay in hospital was significantly less in the coiling group compared with the surgical group.[25] On the national level (UK), coiling has also increased significantly after ISAT according to the National Study of Subarachnoid Hemorrhage, which was conducted by the Royal College of Surgeons of England in cooperation with the Society British of Neurological Surgeons and The British Society of Neuroradiologists.[26] This national study was carried out in 34 neurosurgical units across the UK and Ireland and covered the period between September 2001 and September 2002. The number of patients enrolled in this study was 2397: 1269 (53%) were treated by surgical clipping; 905 (38%) by endovascular coiling, and the rest had either wrapping or no treatment. The proportion of patients who underwent coiling increased over the study period. This increase was noticed after the dissemination of the ISAT results (May 2002). The rate of coiling in this study increased from 34% to 54% after the ISAT. This increase was even more pronounced in centers from which the highest number of patients was recruited for the ISAT study (from 49% to 87%). This study, unlike the ISAT reported no difference in the clinical outcomes between coiling or clipping for ruptured intracranial aneurysms (unfavorable outcome was 35% for clipping compared with 34% for coiling).[26] Another study from Europe showed the same trend in the treatment of patients with aneurysmal SAH following the publication of ISAT.[27]

Updates of the ISAT. In September 2005, the ISAT group published its first update of their work in the Lancet.[28] The one-year data were complete for the total number of patients randomized in the study (2143 cases). The difference in the primary outcome (modified Rankin scale of 3-6) remained significant; 23.5% for the coiling group compared with 30.9% for the clipping group, with a 7.4% absolute risk reduction. The risk of seizures following the 2 procedures was reported. In the clipping group, 68 patients (6.35%) developed seizures after discharge compared with 41 patients (3.8%) in the coiled group. Unlike the first 2 outcomes, the third outcome (re-bleeding) was more in favor of surgery. In the 4 years mean follow up recorded by this update, there were 7 cases of late re-bleed after one year

of treatment in the coiling group compared with only 2 cases in the clipping group (**Table** 4). The last results emphasized the results of the first study concerning the one-year clinical outcome. However, it raised more concern regarding the long-term safety of coiling. The same group published another paper in Stroke in 2007,[29] looking into the number of patients in the ISAT cohort who required re-treatment due to residual filling or re-growth of the target aneurysm. The mean follow up was 4 years (up to 7 years). The results of this study showed that re-treatment of the target aneurysm was performed in 191 patients (17.4%) in the coiling group compare to 39 patients (3.8%) in the clipping group. After endovascular treatment, 97 patients (8.8%) were re-treated early (in the first 3 months), 94 (8.6%) late, and 7 patients (0.6%) after rebleeding. The mean time to late re-treatment was 20.7 months. After neurosurgical clipping, 30 patients (2.9%) were re-treated early, 9 (0.85%) late, and 3 (0.3%) after rebleeding. The mean time for late re-treatment was 5.7 months. Late re-treatment was 6.9 times more likely after coiling. Interestingly, from the 94 patients who had late re-treatment in the coiling group, 34 patients were regarded as complete occlusion on the initial follow up angiography and late angiography showed re-growth of the aneurysms. In the surgical group, all 9 patients who had late re-treatment developed re-growth of their aneurysms (**Table 5**). Re-treatment in the coiling group was carried out mainly by surgery (103 patients). While in the clipping group, most patients were treated by coiling (35 patients). After this study, one could argue that coiling might be a safer procedure in terms of clinical outcome, but it does associate with a cumulative risk of repeated treatments and more costs are added with more admissions and complications. To resolve this problem, the ISAT group conducted another study looking at the costs related to the initial and subsequent procedures. The total cost included hospital stay, ICU, equipment, staff, complications, and follow-ups. The data were based on a sub-sample of all patients randomized in the ISAT study across the UK centers (total of 1644 patients). The study calculated the cost of both modalities in the first 24 months of treatment. The results showed no significant difference in the total costs in the first 24-month period. Endovascular patients had higher costs than neurosurgical patients for the initial procedure, subsequent procedures, and follow up angiograms. However, the difference becomes small when the prolonged initial length of stay of the surgical group is added.[30] More recently, 2 of the main members of the ISAT committee participated in a mathematically-based study trying to see whether the risk of late re-bleeding could overturn the superiority of endovascular coiling over surgical clipping seen in the ISAT. In this study, the authors calculated the life expectancy of patients following a SAH and compared it with the life expectancy of those who underwent coiling or clipping in the ISAT cohort. The comparison was divided into different groups depending on the age of the patient. The results of the study showed that patients under the age of 40 treated with coiling will have high risk of late re-bleeding, and this risk would affect their life expectancy significantly. So, despite the better outcome coiling can provide in the first year following treatment, clipping could provide better protection from late re-bleeding, and this is very significant in patients under 40 years old.[31]

Aneurysm surgery after ISAT. Every so often, in the history of medicine a major technical or pharmaceutical innovation leads to a sudden and fundamental shift in practice. In the world of neurology and neurosurgery, the introduction of L-dopa and the CT scan, for example, had an immediate effect on the surgical treatment of Parkinson disease and the disappearance of ventriculography. It seems likely that the innovation of endovascular coiling for intracranial aneurysms has had the same impact on aneurysm surgery.[32] We have shown already in this review the dramatic shift in treating intracranial aneurysms since the publication of ISAT. The neurosurgeons now are facing fewer numbers of aneurysms that are not suitable for endovascular intervention. These are usually difficult, complex, and require more surgical expertise. In a recent review,[33] on the surgical outcome of aneurysms treated in a busy neurosurgical unit between 2002 and 2007 (post ISAT era); the authors found that surgery still has a role in treating aneurysms. Only 20% of aneurysms were unsuitable for coiling and were treated surgically. The common reasons for unsuitability for endovascular treatment were; small aneurysms (less than 2 mm), complex giant ones, wide neck, aberration of intracranial vasculature, incorporation of distal branches in the aneurysm sac, and difficult access. The operative timing was longer, and the number of clips used was higher in these patients compared with the pre ISAT period. In addition, most of these cases had to be performed by a senior neurovascular surgeon. The surgical outcomes were good and comparable with pre-ISAT results. They concluded that ruptured intracranial aneurysms deemed unsuitable for endovascular interventions are also difficult cases to treat surgically and require more surgical experience to maintain good outcomes. These cases, due to their technical complexities, unfortunately, offer limited training potential for the pre-certificate neurosurgical trainee. The management of aneurysmal SAH patients changed after the ISAT study. Ideally, all these patients need to be transfer to highly specialized centers that can provide a surgical neurovascular and endovascular service. The neurosurgeon has to perform a certain number of cases per annum to maintain his experience. At least 20-30 per annum according to the Society of British Neurological Surgeons.[26] Post-certificate training (Fellowship) in neurovascular surgery

is a necessity for neurovascular sub-specialization, and in some countries like the US training in both neurovascular surgery and endovascular techniques is becoming more popular.[34]

In conclusion, coiling techniques have evolved since ISAT, and more difficult aneurysms are treated using new types of coils, stents, balloon remodelling, and so forth.[35,36] In contrast, the development of surgical techniques has remained relatively static since the introduction of the microscope to aneurysm surgery in the late 1970s, yet it is faced with more and more difficult aneurysms to treat. This challenge has recently led to a change in training neurosurgeons, and establishing specialized units with dedicated neurovascular surgeons who can clip or coil themselves, or with interventional neuroradiologists. Many experts now believe that better results can be achieved in specialized centers where each patient is evaluated, and the 2 treatments modalities are used individually or in combination.[37]

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