THE FUTURE MANAGEMENT OF SUBARACHNOID HAEMORRHAGE

Implications of the International Subarachnoid Aneurysm Trial (ISAT)

A.J. MOLYNEUX (1), R.S.C. KERR (2)


Subarachnoid haemorrhage (SAH) from a ruptured aneurysm occurs with an incidence of between 6 and 10 per 100,000 per year [1] with a mean age of 53 years at presentation.

Those patients surviving in good clinical condition have a significant risk of rebleeding in the first month. At the end of one month, approximately 33% of patients will have re-bleed without treatment [2-4], the frequency of re-bleeding declining over subsequent months, re-bleeding is associated with a 60% mortality [3]. There is an overall mortality of about 50% at 6 months if the aneurysm remains untreated. Early treatment of the aneurysm by either surgical or endovascular coiling techniques is effective in preventing this rebleed and thus significantly reducing the mortality.

Until about fifteen years ago, no alternative to craniotomy and surgical clipping was available for the treatment of intracranial aneurysms. The use of detachable balloons was limited to a few centres and operators for selective occlusion of intracranial aneurysms. In 1992 minimally invasive endovascular treatment with Guglielmi detachable platinum coils (GDC) was introduced in Europe following on the initial use in the USA at UCLA medical centre. Since the introduction the device has been used in an increasing proportion of patients. Initially the technique was reserved for patients who presented a high surgical risk because of poor clinical condition, older patients, who have been shown to tolerate craniotomy less well for unruptured aneurysms [5] and patients with aneurysms arising from the basilar artery a location where surgical treatment carries significantly higher surgical risk.

Increasingly this technique is being applied to patients in good clinical grade with accessible surgical aneurysms. So which technique is most appropriate – surgery or endovascular occlusion using coils?

To try and answer this question in a systematic and scientific way, and provide a firm basis for any change in clinical practice that would be both widely accepted and reliably based, a pilot randomised controlled clinical trial was commenced in 1994 in Oxford. Following this successful pilot a full-scale trial, funded by the UK Medical Research Council, commenced in 1997. Additional funding was subsequently provided by the Canadian and French Government medical research bodies.

The International Subarachnoid Aneurysm Trial (ISAT) [6, 7], is an International multi-centre, prospective randomised controlled clinical trial (RCT) involving 44 Neurosurgical Centres mostly from Europe but with some centres in North America and Australia. It compares surgical clipping with endovascular coiling of ruptured aneurysms and seeks to determine which technique results in better outcomes for patients. The primary endpoint is death or disability at one year measured on the modified Rankin scale. The trial has recruited for seven and a half years since the start of the pilot study.

Recruitment into this trial was stopped on the 2nd of May 2002 by the Trial Steering committee, following the release of the un-blinded interim analysis by the Data Monitoring committee. At closure of recruitment 2143 patients have been enrolled.

The primary outcome results of this trial that led to the closure of recruitment into the trial showed that on the cohort of patients analysed with 1 year outcomes there was a 24.3% relative risk reduction at 1 year based on outcomes in 1491 patients at a statistical significance of more than 3 standard deviations (P value < 0.001). Further information and details have been now submitted for publication and should be available in the Lancet by the time
THE FUTURE MANAGEMENT OF SUBARACHNOID HAEMORRHAGE

75

this editorial is published and will be presented at the Symposium Neuroradiologicum.

The results of this trial are applicable to the patient population enrolled in the trial. All randomised trials examine a selected population. Of the enrolled patients in 89% are in good clinical grade (WFNS 1&2) and 97% have anterior circulation aneurysms. The patient group that are usually judged most suitable for surgical treatment.

Further more detailed information we hope will be published in the Lancet by the time of publication of this journal, and details of the primary outcome details will be presented at the Symposium Neuroradiologicum. Complete 1 year follow up of enrolled patients to the primary endpoint is not due until May 2003, and the trial will continue annual follow up of patients until 2007 to establish reliable data for the long term risk of re-bleeding for these patients.

The implications of the stopping of this Trial and the clear-cut result have major consequences for the Neuroradiological and Neurosurgical community worldwide.

The uptake of coil treatment for cerebral aneurysms has varied widely. This has been largely due to various local factors in different countries, availability of the necessary skills, equipment, funding for coils and not least the economic system in which Health Care operates.

In many European countries endovascular coil treatment is provided in most neurosurgical centres by interventional neuroradiologists, and in some of the smaller centres there is no availability for coil treatment of aneurysms. Indeed many centres have only one, or at the most two neuroradiologists capable of performing the procedure. Nevertheless the consequences of the closure of recruitment into the trial has had a sudden and immediate impact on the patterns of care in many UK centres with an immediate switch of practice to coil treatment, even in advance of formal publication, reinforcing a trend that was already occurring.

There are many questions to be addressed from the data that has been accumulated and continues to accumulate during the follow up that will continue for a further 5 years. Provided endovascular treatment it is as robust in the long term as surgery at preventing re-bleeding, it will be increasingly difficult to offer surgical treatment to patients whose aneurysms are suitable for endovascular coil occlusion.

No other new minimally invasive procedure has been subjected to such a large scale and rigorous evaluation in comparison with an existing surgical technique but the ramifications of this study will continue for many years to come and the results are likely to lead to a fundamental shift of the paradigm of aneurysm treatment in many places.

REFERENCES


