TITLE: Endovascular Coiling versus Surgical Clipping: A Review of the Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Subarachnoid hemorrhage (SAH) occurs when there is bleeding into the subarachnoid space.\(^1\) Over 85% of SAH cases occur following the rupture of an intracranial aneurysm, also known as a cerebral aneurysm.\(^1\) This type of SAH is referred to as aneurysmal SAH, or aSAH.\(^1\) Approximately 15% of individuals with aSAH die before reaching the hospital and those who survive are at risk of having another hemorrhage or a cerebral ischemic event.\(^2\) The prognosis of individuals with aSAH is poor; approximately 50% do not survive beyond one month.\(^1\)

The goal of treating aSAH is to prevent blood flow from the artery (occlude) and to prevent re-bleeding.\(^3\) Occlusion of the artery is accomplished using one of two approaches: surgical clipping (SC) or endovascular coiling (EC). SC involves a clip being placed across the neck of the aneurysm to stop blood flow.\(^3\) The SC procedure requires a craniotomy (an operation that requires the removal of a section of the skull to access the brain), which may not be suitable for patients who are of advanced age or who have a poor health status.\(^4\) EC is a minimally-invasive technique that has been used to treat ruptured and un-ruptured intracranial aneurysms since the mid-1990s.\(^4\) EC does not require open surgery and rather, involves the delivery of platinum coils to the lumen of the aneurysm via a catheter using radiological guidance.\(^5\) A local thrombus forms around the coils and the thrombosed aneurysm prevents entry of blood into the aneurysmal space.\(^3\) EC is not indicated for wide-necked aneurysms. SC and EC are used to treat both ruptured and un-ruptured intracranial aneurysms.\(^6\)

EC is being used increasingly as an alternative to SC.\(^7\) This report will review the evidence on the comparative clinical and cost-effectiveness of EC and SC for the treatment of intracranial aneurysms.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of endovascular coiling compared to surgical clipping for patients with cerebral aneurysms?

2. What is the cost-effectiveness of endovascular coiling compared to surgical clipping for patients with cerebral aneurysms?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and August 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Internet links were provided, where available.

To be considered for inclusion, clinical studies had to compare the effectiveness of EC and SC for the treatment of cerebral aneurysms (ruptured or un-ruptured). Reviews were excluded if the methods were not systematic (did not include a search of more than one database and involve article selection by at least two people).

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs) and economic evaluations.

SUMMARY OF FINDINGS:

Two systematic reviews and four economic evaluations were identified. One article reporting on the long-term follow-up of participants in one RCT was also identified. No health technology assessments were identified.

Systematic reviews and meta-analyses

A systematic review by Raja et al. was published in 2008 and evaluated the clinical effectiveness of EC compared with SC for the management of patients with intracranial aneurysms (ruptured or un-ruptured). The literature search was limited to articles published between 1991 and August 2007. The study types eligible for inclusion were RCTs, controlled clinical trials, and observational studies. Studies that evaluated either treatment alone were not included. The primary outcomes of interest were mortality, post-procedure functional status, procedural and post-procedural re-rupture, percent occlusion, and re-treatment. Secondary outcomes of interest included procedural failure and morbidity. Forty-seven studies were included in the review, including two RCTs. The remaining studies were observational. The sample sizes for the observational studies ranged from six patients to 3,919 patients. The two RCTs included 109 patients and 2,143 patients. The authors stated that there was a lack of consistency in reporting of data between studies, therefore it was not possible to perform a meta-analysis. Of the studies reporting patient characteristics, the minimum ages reported ranged from 9 years to 51.5 years and the maximum ages ranged from 47 years to 89 years. Females accounted for 72.3% of participants in the included studies. The authors of the
systematic review reported that 18 of the included studies had clinical outcomes that did not differ in terms of statistical significance between the EC and the SC groups. The results from 18 studies favoured EC and a further 10 studies reported that SC was most effective. It was not stated if these differences were statistically significant. One study did not report if one procedure was more effective than the other. Of the two RCTs included in the systematic review, one did not report a statistically significant difference between the two procedures, while the second RCT published in 2002, the International Subarachnoid Aneurysm Trial (ISAT), found that EC was statistically significantly superior to SC at one year. An article detailing the follow-up of patients enrolled in ISAT was published in 2005 and reported that aneurysms that were managed by SC had a higher rate of complete occlusion and a lower rate of re-bleeding than EC. The systematic review did not state if these differences differed statistically.

Raja et al recommended that both EC and SC should be considered for the treatment of patients with intracranial aneurysms and that the choice between EC and SC may be dependent on the expertise available at the treatment centre, the physical properties of the aneurysm (size and location) and patient characteristics (age and co-morbidities).

In 2005, the Cochrane Collaboration published a systematic review by van der Schaaf et al. comparing the use of EC with SC for the treatment of patients with aneurysmal subarachnoid hemorrhage. The literature search was limited to RCTs published before February 2005. The main outcome of interest was poor outcome (death or decrease in functional status). Other outcomes of interest included all cause mortality, secondary cerebral ischemia, recurrent hemorrhage, complications occurring during or within 24 hours of a procedure, and occlusion rate. A total of three RCTs, two that were published and one that was unpublished, were identified. Both of the published RCTs were discussed in the systematic review by Raja et al. The unpublished RCT included 20 patients. van der Schaaf et al. conducted a meta-analysis that included a total number of 2,272 patients from the three trials (EC=1,135 patients; SC=1,137 patients). The mean age of patients ranged from 49.5 years to 52 years. At one year follow-up, 24% of the patients in the EC group had a poor outcome compared to 31% of patients in the SC group. This absolute risk reduction of poor outcome was statistically significantly different (7% reduction, 95% CI; 4% to 11%). The authors also reported that the risk of recurrent hemorrhage up to one year after the procedure was statistically significantly higher in the EC group.

The authors concluded that if the aneurysm is suitable in terms of size and location for treatment by either EC or SC, then, based on the evidence from one trial, EC is associated with a more favourable outcome.

Randomized controlled trials

A study reporting long-term follow-up results from patients treated in the ISAT was published in 2009 by Molyneux et al. A total of 2,143 patients were randomized originally and 1,582 (EC=813 patients; SC=769 patients) were eligible for follow-up. Some centres participating in the trial did not continue to follow patients beyond five years (EC=87 patients; SC=93 patients). Other reasons for loss of follow-up included death (EC=165 patients; SC=194 patients) and refusal (EC=8 patients; SC=14 patients). The mean follow-up time was nine years (range: six years to 14 years). The relative risk of death at five years was based on follow-up data available for 867 patients in the EC group and 857 patients in the SC group. The relative risk of death was significantly lower in the EC group (0.77, 95% CI; 0.61 to 0.98). The proportion of patients at five years who were able to function independently did not differ between groups.
The authors reported that the annual risk of re-bleeding was statistically significantly higher in the EC group than in the SC group when analysis was based on data from patients available for follow-up. This difference was not statistically significant when analysis was conducted on the intention-to-treat group. The authors concluded that the risk of re-bleeding from a coiled aneurysm was small. Four of the authors cited possible conflicts of interests.

**Economic evaluations**

Maud et al. (2009)\(^{10}\) compared the cost-effectiveness of EC and SC in patients with ruptured intracranial aneurysms at one year post-treatment. The ISAT was used to obtain clinical data including rate of re-bleeding and re-treatment, quality of life information, and patient characteristics. The calculated total costs included initial hospitalization, disability (moderate to severe disability and associated costs with hospitalization, and loss of productivity), angiography, re-treatment, and re-bleeding. Cost-estimates were obtained through relevant literature and from the Premier Perspective Comparative Database (2005-2006) which tracks resource utilization from over 600 hospitals in the United States. It was not stated if these values were discounted. The authors used a Monte Carlo simulation of 10,000 replicates to incorporate uncertainty. The median estimated costs were US$45,493 for EC and were US$41,769 for SC. The cost per quality-adjusted life year (QALY) was US$65,424 for EC and US$64,824 for SC. The median estimated incremental cost-effectiveness ratio (ICER) per QALY gained for patients treated with EC versus SC was US$72,872. This report was based on clinical data obtained at one year follow-up, post-procedure. Long-term follow-up from the ISAT reported a statistically significant increase in re-bleeding in patients treated with EC versus those treated with SC (using an intention-to-treat analysis) at follow-up times between 6 years and 14 years.\(^{9}\) The costs associated with managing re-bleeding may impact the cost-effectiveness. The authors concluded that EC is more costly than SC. The authors suggested that ICER for EC would likely decrease in the future and eventually reverse (in favour of EC) with the accrual of additional patient years with more favourable outcomes status.

Wolstenholme et al. (2008)\(^{11}\) detailed the costs associated with treatment of intracranial aneurysms with either EC or SC. The data were based on a sub-sample of UK-based patients enrolled in the ISAT (1,602 patients with complete follow up to 24 months). The costs associated with the initial and subsequent procedures (ward days, intensive treatment unit days, equipment, staffing, operating room, and consumables) were calculated for the period of 24 months following randomization in the ISAT. The costs were derived from 2004 information and were discounted at a rate of 3.5%. EC was associated with increased costs for the initial procedure and subsequent procedures (including angiograms) compared to SC. EC had lower costs associated with length of stay compared to surgical treatment. The authors concluded that there were no statistically significant differences in the costs between EC and SC at 12 months or 24 months.

The direct costs associated with EC and SC for the treatment of un-ruptured aneurysms was compared by Halkes et al. (2006).\(^{12}\) The study was retrospective in nature and took place in The Netherlands. The study calculated the treatment-related costs of patients (46 patients) who with un-ruptured aneurysms who received either EC (23 patients) or SC (23 patients) over a five-year period. The mean age of patients in the EC group was 53.9 years (83% female) and was 49.7 years (74% female) for the SC group. The costs associated with pre-admission diagnostic procedures, initial procedures (equipment, staffing, operating room time, ward days, intensive care days, laboratory tests, and consumables), and follow-up with angiography at six and 18 months following patients receiving EC treatment. All costs are presented in Euros. The costs were derived from 1999 information and discounted to 2001 costs (discounting rate not stated).
The mean cost was €10,370.29 for EC and was €8,865.42 for SC. The higher cost of EC was mainly due to the material costs of the coils (approximately €5,300) compared with the material costs of SC (€690). The higher material costs for EC were defrayed by reduced costs associated with length of stay (10.5 days for SC patients versus 3.4 days for EC patients) and time spent in intensive care (1.2 days for SC patients versus 0 days for EC patients). Despite the reduction in hospital stay in patients treated with EC, costs were still higher by approximately €1,553. The authors did not include costs associated with complications or with re-treatment in their calculation.

Javadpour et al. (2005) reported on a subset of patients from the ISAT who were treated at a Canadian centre. The total costs of treatment during inpatient stay were calculated for both the EC and the SC groups. A total of 62 patients with ruptured aneurysms (EC=30 patients; SC=32 patients) were enrolled in the ISAT at the Canadian site. The mean age did not differ significantly between groups (51 years). Forty percent of the patients in the EC group were male and 28% of the patients were male in the SC group. The costs included intensive care unit stay, ward days, laboratory tests, imaging studies, procedural costs (EC or SC) including materials, and the costs of angiographic follow-up at six months for patients in the EC group. Physician fees, costs associated with rehabilitation, and costs associated with future procedures such as completing aneurysm obliteration were not factored into the total procedural costs. The costs were calculated during the period of 1998 and 2002. The authors concluded that there were no significant differences in the total treatment costs between EC and SC for the treatment of ruptured intracranial aneurysms. The authors further suggested that the high procedural costs of EC were off-set by the decrease in length of stay. This study did not include costs associated with follow-up beyond six months and therefore, costs associated with re-treatment and re-bleeding were not considered.

Limitations

Two systematic reviews were identified by the literature search. The majority of the studies included in one systematic review were observational. Observational studies may not control for potential bias. There were few studies identified that were associated with high internal validity (e.g. randomization of interventions). A total of three RCTs were identified by the included systematic reviews and all three were published outside the date restriction of the current report.

One economic evaluation was conducted in Canada. The information reported in the other economic studies may not be generalizable to the Canadian health care system. The inclusion of costs was limited to those accrued during in-patient stay and during six-month radiological follow-up for EC patients. Three of the four economic evaluations obtained the clinical data from the same trial (ISAT). Information regarding the clinical effectiveness of EC and SC for the treatment of un-ruptured intracranial aneurysms is more limited than ruptured aneurysms.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The two included systematic reviews appraised a total of three RCTs comparing EC to SC for the treatment of intracranial (cerebral) aneurysms. One systematic review concluded that the choice of treatment should be made based on the available expertise (i.e. neurosurgeons and interventional radiologists), the size and location of the aneurysm, and patient characteristics that may influence outcome (i.e. age and co-morbidities). The second systematic review concluded that clinical outcomes of EC at one year following treatment were more favourable.
than SC, based on the evidence from one RCT (ISAT) of over 2,000 patients with ruptured intracranial aneurysms.

An article published by the lead investigators of the ISAT reported data for long-term follow-up. EC was associated with a significant decrease in mortality at five years post-treatment. The authors reported that the annual risk of re-bleeding did not differ statistically between the EC and SC groups when the analysis was performed on the intention-to-treat population. The annual risk of re-bleeding was significantly higher in the EC group compared to the SC group when the analysis was performed on the sample size available at time of follow-up. Overall, limited evidence from two systematic reviews suggested that the short-term outcomes (up to one year) of EC for the treatment of intracranial aneurysms may be comparable to SC. The evidence regarding the long-term outcomes of patients treated with either EC or SC suggest that occurrence of re-bleeding may be higher in the EC group.

The majority of the economic evaluations were based on the clinical data reported in the ISAT. Two of the evaluations noted that the cost of treatment of intracranial aneurysms with EC was higher than treatment with SC. One of these studies included both direct and indirect costs for a follow-up period of one year, while the other calculated direct costs including follow-up for EC patients at six and 18 months. The remaining two studies, including one Canadian evaluation, reported that there were no significant differences between the calculated direct costs for either procedure. Of the latter two studies, one reported a non-significant increase in cost for the EC group taking in account follow-up costs at 24 months. The second, the Canadian study, limited the calculation of follow-up costs to angiography at six months for EC patients and did not calculate any anticipated costs from re-treatment or re-bleeding. Results from the Canadian study may represent an under-estimate of total costs.

In general, the evidence regarding the clinical effectiveness of EC compared with SC suggests that the two procedures may have comparable clinical effectiveness at one year follow-up. Treatment with EC beyond one year is associated with increased need for re-treatment and incidence of re-bleeding. The economic evaluations suggested that the cost of EC was higher than SC and that this increase was mainly due to the cost of the platinum coils. All economic evaluations reported that EC was associated with lower in-hospital stay costs. It is possible that the cost of the coils may decrease in the future as the number of manufacturers increase. The choice of EC or SC for the treatment of aneurysms may depend on the expertise available at a particular medical centre (i.e. interventional radiology or neurosurgery), the physical characteristics of the aneurysm (i.e. location and size), and the health status of the patient.

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