Coil Embolization versus Clipping for Ruptured Intracranial Aneurysms: A Meta-Analysis of Prospective Controlled Published Studies

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ABSTRACT

BACKGROUND AND PURPOSE: Coil embolization is an alternative to clipping for intracranial aneurysms. However, controversy exists regarding the best therapeutic strategy in patients with ruptured aneurysms, and there is great center- and country-related variability in the rates of clipping versus coiling. We performed a meta-analysis of prospective controlled trials of clipping versus coil embolization for ruptured aneurysms.

MATERIALS AND METHODS: We performed a search of the English literature for published prospective controlled trials comparing surgical clipping with endovascular coil embolization for ruptured intracranial aneurysms. Data were abstracted from the identified references. Outcomes of interest were the proportion of patients with a poor outcome at 1 year and episodes of rebleeding from the index treated aneurysm after the allocated treatment.

RESULTS: There were 3 prospective controlled trials eligible for inclusion. These studies enrolled 2723 patients. Meta-analysis of these studies showed that the rate of poor outcome at 1 year was significantly lower in patients allocated to coil embolization (risk ratio, 0.75; 95% confidence interval, 0.65–0.87). This relative effect is consistent with an absolute risk reduction of 7.8% and a number needed to treat of 13. The effect on mortality was not statistically different across the 2 treatments. Rebleeding rates within the first month were higher in patients allocated to endovascular coil embolization.

CONCLUSIONS: On the basis of the analysis of the 3 high-quality prospective controlled trials available, there is strong evidence to indicate that endovascular coil embolization is associated with better outcomes compared with surgical clipping in patients amenable to either therapeutic strategy.

ABBRévIATIONS: RCT = randomized clinical trials; GDC = Guglielmi detachable coil; GOS = Glasgow Outcome Scale; ISAT = International Subarachnoid Aneurysm Trial; BRAT = Barrow Ruptured Aneurysm Trial

R ebleeding from a ruptured aneurysm is a deadly complication. Early treatment of the ruptured aneurysm has been proved to reduce the risk of early rebleeding1 and has been the standard strategy for the treatment of patients with subarachnoid hemorrhage over the past 3 decades.2 With the development of neuroendovascular techniques, endovascular coil embolization has become a valid and increasingly used alternative to surgical clip obliteration in patients with ruptured intracranial aneu-

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Table 1: Summary of published randomized clinical trials of surgery versus coiling for ruptured aneurysms

|                  | Kuopio 7  | ISAT 8  | BRAT 9  |
|------------------|-----------|---------|---------|
| Period           | February 1995 to August 1997 | 1997 to September 2002 | March 2003 to January 2007 |
| Single-center/multicenter Enrollment | Single <72 hours | Multicenter <28 days | Single <14 days |
| Total patients screened | 242 | 9559 | 725 |
| Patients enrolled | 109 | 2143 | 471 |
| Mean age (years) | Endovascular 49 | 52 | 54 |
|                   | Surgery 50 | 52 | 53 |
| No. of patients allocated endovascular treatment | 52 | 1073 | 233 |
| No. of patients allocated surgical treatment | 57 | 1070 | 238 |
| Good grade, n (% of total) | 93 (85.3) | 2018 (94.2) | 380 (80.7) |
| Poor grade, n (% of total) | 16 (13.7) | 94 (5.8) | 91 (19.3) |
| Crossovers | From endovascular to surgery 12 | 9 | 75 |
|            | From surgery to endovascular 4 | 38 | 4 |

Statistical Analysis. Random effects model was used to pool relative risks (risk ratios) and 95% confidence intervals across studies. Heterogeneity was evaluated by using the I² statistic.

RESULTS

Three prospective controlled studies were eligible for inclusion in this analysis. Table 1 summarizes the main study characteristics, methodology, and enrollment. These studies enrolled 2723 patients. Only patients with aneurysms amenable to either surgical or endovascular treatment were enrolled in 2 of the trials, whereas in the remaining trial, all consecutive patients with SAH (including nonaneurysmal SAH) who agreed to participate in the study were randomly assigned to 1 of the 2 treatment modalities in an alternating fashion. Functional outcome at 1 year was reported in the 3 studies.

This was performed by use of the GOS (poor outcome defined by GOS 1–3) rated by 1 of the investigators in 1 study; by use of modified Rankin Scale (poor outcome defined by modified Rankin Scale score 3–6) assessed by the patients in a mailed questionnaire (or a caretaker if the patient was unable to complete it) in 1 study; and by use of modified Rankin Scale rated by a research nurse in 1 study. Methods of assessment of outcome at 1 year, rates of poor outcome according to treatment allocation, and episodes of rebleeding are summarized in Table 2.

DISCUSSION

Since the introduction of GDCs into clinical practice in 1992, 2 randomized trials and 1 prospective controlled clinical trial have been published comparing functional outcome at 1 year after coil embolization versus surgical clip ligation for ruptured intracranial aneurysms. Our meta-analysis of these published trials shows that the rate of poor outcome is significantly lower in patients allocated to coil embolization (risk ratio, 0.75; 95% confidence interval, 0.65–0.87) than after surgical clip ligation. Furthermore, subgroup analyses of the clinical trials have indicated that the risks of seizures, delayed cerebral ischemia, ischemic lesions on MR imaging, and in-hospital complications are lower after coil embolization than after surgical clip ligation. A subgroup analysis of patients enrolled in the ISAT also showed improved cognitive outcome after coil embolization compared with surgery. These observations provide convincing evidence that endovascular coil embolization should be considered a treatment option for patients with SAH.
strongly considered as the preferred treatment technique for a ruptured aneurysm amenable to either therapeutic technique (surgery or endovascular coiling).

The "Kuopio" study was the first of the 3 published prospective controlled studies of coil embolization versus clip ligation for ruptured intracranial aneurysms. The trial was a single-center study conducted in Kuopio, Finland, between 1995–1997 shortly after the introduction of endovascular treatment in that center. The study enrolled patients with aneurysms amenable to either surgical or endovascular treatment; patients requiring urgent hematoma evacuation or with a geometry not amenable to coil embolization were excluded. Overall, 109 patients were randomly assigned to surgery (57 patients) or endovascular treatment (52 patients). Primary clinical outcome at 1 year (measured by the GOS) was not significantly different between the 2 groups (intent-to-treat analysis), though there was a trend toward a lower rate of poor outcome in patients undergoing endovascular treatment (23% versus 33% in those allocated to surgery). There was 1 episode of early rebleeding after incomplete coil embolization, but no episodes of rebleeding were observed after discharge during a mean follow-up of 4 years.

ISAT was a large, multicenter, randomized trial to assess the effectiveness of coil embolization compared with surgical clip ligation. The study was conducted between 1997–2002, and it was halted prematurely after enrollment of 2143 patients because of a significant outcome difference between the 2 groups favoring endovascular coil embolization. In ISAT, the proportion of patients with a poor outcome at 1 year (defined as a modified Rankin Scale score of 2) was 23.5% among patients assigned to coil embolization versus 30.9% in those allocated to surgery. There was 1 episode of early rebleeding after incomplete coil embolization, but no episodes of rebleeding were observed after discharge during a mean follow-up of 4 years.

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tients with poor grade SAH and posterior circulation aneurysms being treated preferentially by coil embolization in ISAT centers. Publication of the results of ISAT changed practice patterns for the treatment of ruptured aneurysms. However, several questions remained unanswered. Given the relatively high number of screened patients who were not considered candidates to participate in ISAT, some questioned the applicability of the ISAT results to patients with aneurysmal SAH at large. Moreover, questions were raised whether the ISAT results could apply to North American centers, where a supposedly higher degree of subspecialization exists among cerebrovascular surgeons dedicated to the care of patients with ruptured intracranial aneurysms.

In response to these concerns, investigators at the Barrow Neurological Institute in Phoenix, Arizona, launched BRAT in 2002. To assess results in a “real-world” situation, the BRAT investigators randomly assigned in an alternate fashion every patient with SAH admitted to their center during the period of the study who agreed to participate. As a consequence of this design, many patients with nonaneurysmal SAH were entered in the trial. Similarly, a large number of patients allocated to endovascular treatment crossed over to surgical treatment because patients could be enrolled regardless of whether the aneurysm was amenable to both treatment modalities. As a consequence, aneurysms that could not safely be treated with coiling because of technical reasons (ie, very small aneurysms) or clinical considerations (ie, aneurysms associated with intraparenchymal hematomas necessitating surgical evacuation) were originally assigned to embolization. Despite this high rate of crossover, the BRAT study confirmed the ISAT conclusions: outcomes at 1 year were better after coil embolization than after surgical clipping. The proportion of patients with a poor outcome (defined by modified Rankin Scale score >2) was 33.7% in the surgical group versus 23.2% (P = .02, intention-to-treat analysis) in the endovascular group. As-treated analysis yielded similar results, with 33.9% of patients in the surgical group and 20.4% in the endovascular group with a poor outcome at 1 year (P = .01).

Endovascular coil embolization of ruptured intracranial aneurysms is associated with better outcomes, but the risk of aneurysm recurrence, the need for retreatment, and the risk of rebleeding from the index aneurysm are higher after coil embolization. Among patients enrolled in ISAT, 17.4% of those undergoing endovascular treatment required re-treatment because of recurrence/residual aneurysm. Likewise, the risk of rebleeding was higher after endovascular coil embolization. Rates of rebleeding were 3.0% during the first year and 0.3% per year between post-treatment years 2 and 6, with no episodes of rebleeding after year 6. Despite the higher risk of rebleeding, the initial beneficial effect on functional outcome remained present up to 7 years after treatment, except in the subgroup of very young patients (<40 years).

It is possible that the clinical results from endovascular treatment and the degree of long-term protection afforded by coil embolization have improved over the last decade, (ie, since the completion of ISAT) because of increasing operator experience and development of better devices. This argument is supported by the fact that there were no episodes of rebleeding reported in BRAT for up to 2 years after endovascular therapy. Similarly, results of prospective studies comparing different coil designs have recently reported better outcomes after coil embolization than those reported in ISAT.

Although this meta-analysis of the 3 published randomized clinical trials unequivocally indicates that outcomes at 1 year are better with endovascular treatment, there continue to be patients who are better candidates for surgical clip ligation. Very small aneurysms are often challenging to treat with an endovascular approach. Similarly, many middle cerebral artery aneurysms have an unfavorable geometry for primary coiling, and they are often better treated with surgical clipping. Moreover, very young patients with ruptured anterior circulation aneurysms (especially those who may be noncompliant with follow-up imaging) may also be better candidates for surgical treatment rather than endovascular coil embolization. Despite the evidence from randomized clinical trials, the decision on what is the best treatment for a ruptured aneurysm in a given patient should be individualized by taking into consideration aneurysm-related and patient-specific factors.

We acknowledge that our meta-analysis has limitations. The methodologic quality of the trials included was variable. Only ISAT fulfilled all the criteria of a high-quality randomized controlled trial. Entry criteria and outcome assessment differed across studies. Yet, the finding that all trials produced consistent results favoring the endovascular arm reassures us that these methodologic differences do not negate the validity of the meta-analysis.

**CONCLUSIONS**

This meta-analysis of published prospective controlled trials of surgical clipping versus endovascular coil embolization for patients with ruptured intracranial aneurysms provides convincing evidence that functional outcome at 1 year is better after endovascular treatment despite a higher risk of rebleeding from the index aneurysm after coil embolization. Hence, when technically feasible, endovascular coil embolization should be the preferred technique for the treatment of ruptured intracranial aneurysms.

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