Effects of Timing of Coil Embolization after Aneurysmal Subarachnoid Hemorrhage on Procedural Morbidity and Outcomes

Gerasimos S. Baltsavias, M.D.,
James V. Byrne, F.R.C.S., F.R.C.R., Jim Halsey, B.Sc.,
Stuart C. Coley, M.R.C.P., F.R.C.R.,
Min-Joo Sohn, M.Sc., Andrew J. Molyneux, F.R.C.R.

Department of Radiology (GSB, JVB, SCC, MJS, AJM) and Clinical Trials Service Unit (JH), Radcliffe Infirmary National Health Service Trust, Oxford, England

OBJECTIVE: To elucidate the effect of treatment timing on procedural clinical outcomes after aneurysmal subarachnoid hemorrhage (SAH) for patients treated by endosaccular coil embolization.

METHODS: A group of 327 patients who were consecutively treated, during a 46-month period, for ruptured intracranial aneurysms by coil embolization within 30 days after SAH were evaluated. Outcomes were assessed by comparing immediate pretreatment World Federation of Neurological Surgeons (WFNS) grades, 72-hour posttreatment WFNS grades, and modified Glasgow Outcome Scale scores at 6 months for patients treated within 48 hours (Group 1), 3 to 10 days (Group 2), or 11 to 30 days (Group 3) after SAH.

RESULTS: The three interval-to-treatment groups included 33, 38, and 29% of the patients, respectively. Before treatment, 70% of the patients in Group 1, 78% of those in Group 2, and 83% of those in Group 3 were in good clinical grades (i.e., WFNS Grade 1 or 2). After coil embolization, the WFNS grades were either unchanged or improved for 93.5% of the patients in Group 1, 89.5% of those in Group 2, and 91.5% of those in Group 3. After 6 months, 81.3% of the patients in Group 1 experienced good outcomes (modified Glasgow Outcome Scale scores of 1 or 2), as did 84% of those in Group 2 and 80% of those in Group 3. No statistical difference was demonstrated between the three groups when they were compared for these two variables.

CONCLUSION: The interval between endovascular treatment and SAH did not affect periprocedural morbidity rates or 6-month outcomes. Coil embolization should therefore be performed as early as possible after aneurysmal SAH, to prevent aneurysmal rerupture. (Neurosurgery 47:1320–1331, 2000)

Key words: Embolization, Endovascular treatment, Guglielmi detachable coil, Intracranial aneurysm, Subarachnoid hemorrhage, Timing of treatment, Vasospasm

Aneurysmal rebleeding and delayed ischemic neurological deficits attributable to clinical vasospasm are major causes of morbidity among patients who survive the initial effects of aneurysmal rupture (1, 7, 22, 25). The optimal timing of surgery for acutely ruptured aneurysms is still the subject of debate, because of the effects of vasospasm, which most commonly occurs 3 to 10 days after ictus and has a detrimental effect on patient outcomes. The International Cooperative Study on the Timing of Aneurysm Surgery suggested that results depended on the time interval between treatment and subarachnoid hemorrhage (SAH) (12). Early surgery reduced the risk of rebleeding, but the technical results of surgery were better when surgery was delayed until at least 10 days after SAH. Overall, the advantages of delayed surgery were negated by rebleeding during the preoperative period. Therefore, 6-month outcomes after early surgery were equivalent to those after delayed surgery. The least favorable surgical results were associated with surgery performed between Days 7 and 10 after ictus, i.e., during the period of greatest susceptibility to vasospasm (13).

Since the introduction of electrolytically detachable coils in 1991 (10), endovascular treatment (EVT) has assumed increasing importance in the management of intracranial aneurysms, including those presenting after acute rupture (3, 8, 9, 23, 28, 29). To date, reports of EVT have focused on its role, safety, and efficacy, compared with surgical clipping (2, 5, 15, 19, 23).

Some reports considered the effects of EVT on vasospasm and demonstrated that treatment does not increase the incidence of clinical vasospasm or its consequences (9, 18, 20, 24, 32). However, the potential effects of treatment timing on procedure-related morbidity rates or patient outcomes were not specifically considered in these reports.

It therefore remains to be demonstrated whether treatment timing influences patient outcomes after EVT, as it does after microsurgical clipping. In an attempt to answer this question, we studied the effect of the interval to treatment (ITT) after SAH on procedure-related morbidity rates and outcomes.

PATIENTS AND METHODS

During a period of 46 months (January 1995 to October 1998), 617 patients referred to the Radcliffe Infirmary (Oxford, England) were demonstrated to have at least one intracranial aneurysm by intra-arterial digital subtraction angiography (IA-DSA). Data for patients fulfilling the following criteria were prospectively collected for retrospective review. The study entry criteria were as follows: 1) clinical diagnosis of SAH, supported by computed tomographic findings or a xanthochromic cerebrospinal fluid sample, and at least one aneurysm demonstrated by IA-DSA and 2) coil embolization by endosaccular packing completed within 30 days after the last hemorrhaging episode. Patients who had undergone neurosurgical interventions (except for a cerebrospinal fluid drainage procedure or placement of an intracranial pressure monitor) were excluded.

Of the total of 617 possible patients, 327 (53.5%) fulfilled the criteria and constitute the cohort for this study. The study population included 215 female (65.7%) and 112 male (34.3%) patients (female/male ratio = 1.9:1). The mean age at presentation was 50.5 years (median, 51 yr; range, 11–82 yr). The age distributions according to decade are presented in *Table 1*. The reasons for nonselection were as follows. One hundred ninety-eight patients (32%) were treated by surgical clipping of the ruptured aneurysm (14 of whom were treated after failed EVT, because the aneurysm neck proved to be too wide to retain coils). Sixty-nine patients (11%) were treated by EVT but were excluded because they had undergone recent craniotomies and failed clipping (16 patients) or were treated more than 30 days after SAH (53 patients) because of late referral. Twenty patients (3%) were treated conservatively because of poor neurological condition (EVT was attempted for three of these patients but abandoned after failure to catheterize the aneurysm, because of vasospasm for two patients and tortuous proximal vessels for one patient). Three patients (0.5%) were excluded because of incomplete data.

Patient selection

Patients were selected for EVT after consultation between neurosurgeons and endovascular therapists. Patients were selected firstly on the basis of an angiographic assessment of the aneurysm and the likely difficulty of clipping or EVT and secondly on the basis of clinical status and fitness to undergo treatment. The aneurysm size and location were factors in selecting patients for clipping; for EVT, an assessment was made regarding whether the neck of the aneurysm was sufficiently narrow to retain coils and whether embolization could be performed without compromising the parent artery or adjacent arteries. During the study period, 66 patients with anterior circulation aneurysms suitable for either surgical clipping or EVT, after the aforementioned assessment, were offered entry into an ongoing multicenter randomized trial (International Subarachnoid Aneurysm Trial) and, after providing informed consent, were randomly allocated to EVT.

Treatment

EVT was performed using electrolytically detachable platinum coils (Guglielmi detachable coils; Target Therapeutics, Freemont, CA), which were delivered to pack the body of the aneurysm sac as densely as possible and thus to obstruct the neck. Our procedural protocol has been previously described (2). For patients with multiple aneurysms, the aneurysm thought to have bled was treated first and coincidental aneurysms were treated during the same procedure or later. When, after radiological assessments, doubt remained regarding which aneurysm had ruptured, a craniotomy was performed or all aneurysms were treated by EVT.

Timing of treatment

Coil embolization was performed as soon as possible after selection on the aforementioned basis. Selection occurred as soon as practical after admission to our center, which is a tertiary referral hospital for patients requiring neurosurgery or specialist neurological assessment and treatment. Most patients were treated within 24 hours after transfer. EVT was not delayed because of poor clinical conditions, and treatments were performed on weekends, if necessary. Furthermore, EVT was not postponed or refused because IA-DSA indicated vasospasm. However, if the condition of the patient was unstable, then EVT was delayed until the patient exhibited improvement. The ITT after SAH was 0 to 2 days for 107 patients (33%), 3 to 6 days for 79 patients (24%), 7 to 10 days for 46 patients (14%), 11 to 15 days for 43 patients (13%), and 16 to 29 days for 52 patients (16%). These data are graphically

TABLE 1. Age Distribution of Patients, According to Decade

	11–20 yr	21–30 yr	31–40 yr	41–50 yr	51–60 yr	61–70 yr	71–80 yr	81–90 yr
No. of patients	2	17	45	90	104	50	18	1

presented in *Figure 1*. The reasons for prolonged ITTs were delays in diagnosis and/or transfer to our center.

Data collection

Details of the patients and their treatments were recorded prospectively in a specifically created electronic database. The World Federation of Neurological Surgeons (WFNS) grading scale was used to classify the neurological status of patients at the time of treatment (pretreatment WFNS grade) and 72 hours after the procedure (posttreatment WFNS grade) (31), and a modified Glasgow Outcome Scale (MGOS) was used to document outcomes after 6 months of follow-up monitoring (11).

Because referrals were made by both local and distant neurosurgeons, this series is similar to other reports from tertiary referral centers, in that it includes a relatively high proportion (77%) of patients in good-grade condition and a wide distribution of treatment times. Because we could not verify the WFNS grade at the time of presentation to the hospital for all patients, we recorded the WFNS grade at the time of treatment, i.e., after selection for EVT. Additional data on aneurysm location and size, procedural details, complications, and vasospasm documented by IA-DSA were recorded.

Aneurysm location

The locations of aneurysms assumed to have ruptured are presented in *Table 2*. Ninety-three aneurysms (28.5%) were located in the posterior cerebral circulation. This demographic result reflected our selection practice. Of the putative ruptured aneurysms, 235 (71.8%) were small (<11 mm), 89 (27.2%) were large (11–24 mm), and 3 (0.9%) were giant (>24 mm).The primary aneurysm was treated in one session for all except four patients, for whom treatment required two sessions.

Seventy-six patients (23%) had multiple aneurysms. Sixty-two patients had 2 aneurysms, 10 patients 3 aneurysms, 2 patients 4 aneurysms, and 2 patients 6 aneurysms. In all, 98 coincidental aneurysms were diagnosed, and 33 of these were treated at the same time as the putative ruptured aneurysm. Of the 51 patients left with untreated coincidental aneurysms after acute treatment, 13 patients were treated by EVT within 6 months without complications, 9 patients were treated by EVT after 6 months, and 29 patients have not received any other treatment.

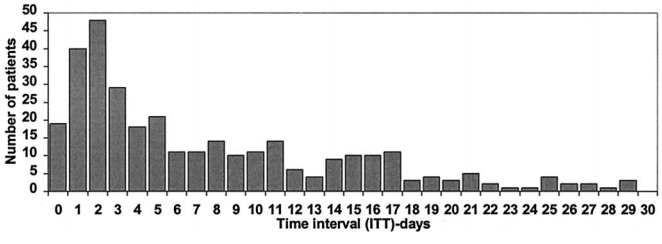

FIGURE 1. Number of patients treated at different times after SAH.

TABLE 2. Locations of Ruptured Aneurysms Treated by Coil Embolization[a]

Location	No.
ICA	28
PComA	55
MCA	53
A1-AComA-A2	97
BA termination	61
BA trunk	10
PCA	3
PICA	13
VA	7
Total	327

[a] ICA, internal carotid artery; PComA, posterior communicating artery; MCA, middle cerebral artery; AComA, anterior communicating artery; BA, basilar artery; PCA, posterior cerebral artery; PICA, posteroinferior cerebellar artery; VA, vertebral artery.

Follow-up monitoring

Patients were monitored by clinical review (usually at the time of follow-up IA-DSA) or by mailed questionnaire. Information on 10 patients was obtained by telephone calls to the patients or their general practitioners. The questionnaire was designed to provide sufficient information for an assessment of outcomes, using a MGOS. Patients were assigned a MGOS score of 1 if they had no symptoms or symptoms that did not interfere with their daily lives, a MGOS score of 2 if they had symptoms that caused some changes in their daily lives but they were independent, a MGOS score of 3 if their symptoms caused significant changes in their daily lives and they required help from other people, a MGOS score of 4 if they were severely handicapped and required constant attention, and a MGOS score of 5 if they had died.

Follow-up periods of at least 6 months were recorded for 322 patients; for 5 patients, follow-up monitoring was limited to an assessment of outcome at the time of discharge from the hospital. There were no procedural complications for these five patients, who did not exhibit changes in WFNS grade after the procedure. The pre- and posttreatment grades for these patients who were lost to follow-up monitoring were WFNS Grade 1 or 2 for two patients and WFNS Grade 3 or 4 for three patients.

Statistical analysis

For the purpose of statistical analysis, patients were divided into three groups according to ITT. Patients who were treated within 48 hours after SAH (Days 0–2) were assigned to Group 1, those treated between Days 3 and 10 were assigned to Group 2, and those treated between Days 11 and 30 were assigned to Group 3. These intervals were chosen to allow comparisons with subjects of the International Cooperative Study (12).

Because the variables being studied were either categorical or ordinal, cross-tabulations and the χ^2 test were used to detect the strength of corresponding associations between the variables. The Mantel-Haenszel χ^2 test was used where ap-

TABLE 3. Comparison of Pretreatment World Federation of Neurological Surgeons Grades for the Three Interval-to-Treatment Groups[a]

WFNS Grade	No. of Patients				P (χ^2)	P (M/H χ^2)
	0–2 d	3–10 d	11–30 d	Total		
1–2	75 (70%)	98 (78.4%)	79 (83%)	252 (77%)	0.08	0.04[b]
3–5	32 (30%)	27 (21.6%)	16 (17%)	75 (23%)		
Total	107 (33%)	125 (38%)	95 (29%)	327 (100%)		

[a] M/H, Mantel-Haenszel; WFNS, World Federation of Neurological Surgeons.
[b] Trend to significance.

TABLE 4. Comparison of Incidence of Rebleeding among All Patients before Endovascular Treatment for the Three Interval-to-Treatment Groups[a]

	No. of Patients				P (χ^2)	P (M/H χ^2)
	0–2 d	3–10 d	11–30 d	Total		
Single hemorrhage	86 (80%)	105 (84%)	87 (92%)	278 (85%)	0.08	0.02[b]
Rebleeding before EVT	21 (20%)	20 (16%)	8 (8%)	49 (15%)		

[a] M/H, Mantel-Haenszel; EVT, endovascular treatment.
[b] Trend to significance.

propriate (i.e., for the ordinal data), to look for possible trends among the variables. Analysis of variance was used to compare the mean ages of patients in the three ITT groups.

RESULTS

Treatment timing groups

The three groups of patients with different ITTs included 107 patients (33%) in Group 1, 125 patients (38%) in Group 2, and 95 patients (29%) in Group 3. The groups were compared for potential confounding factors that might have introduced a selection bias. The variables chosen were age, pretreatment WFNS grade, rebleeding before treatment, and angiographic vasospasm.

The mean patient ages were 48.9 years (Group 1), 49.2 years (Group 2), and 54.2 years (Group 3) for the three ITT groups. The mean patient age for Group 3 was greater than those for the other two groups (for which mean ages were not statistically different). We do not consider this difference to have caused a bias in the study, because there was no significant correlation between age and outcomes.

The pretreatment clinical conditions of the patients were compared for the three ITT groups. Those in pretreatment WFNS Grades 1 or 2 (i.e., good grades) and 3, 4, or 5 (i.e., poor grades) were combined for this and subsequent comparisons. Comparisons of WFNS grades for the three ITT groups demonstrated that the grades were statistically similar ($P = 0.08$, χ^2 test) and the distribution of patients in good and bad grades was not biased to any particular ITT group (*Table 3*). There was a trend for better grades in the late-treatment group (Group 3, treatment 11–30 d after SAH) with the Mantel-Haenszel χ^2 test for trend ($P = 0.04$), confirming the natural history of recovery (and therefore better grades) after SAH.

There was a higher incidence of more than one bleeding episode among ITT Group 1 patients (*Table 4*). The χ^2 test did not indicate a statistically uneven distribution of this complication ($P = 0.08$), but the Mantel-Haenszel test confirmed a trend for a lower incidence of rebleeding in the late-treatment Group 3. This trend, we assume, reflects firstly the fact that rebleeding is more frequent in the acute period and secondly our practice of treating patients as soon as possible after referral, which was sometimes expedited after rebleeding.

The three groups varied in their incidence of angiographic vasospasm at the time of treatment (*Table 5*). Angiographic vasospasm was statistically more frequent in Groups 2 and 3 than in Group 1. This was confirmed as a trend among the three groups with the Mantel-Haenszel test ($P = 0.01$). The potential bias of these data is discussed below.

TABLE 5. Comparison of Angiographic Vasospasm among Patients in the Three Interval-to-Treatment Groups[a]

	No. of Patients				P (χ^2)	P (M/H χ^2)
	0–2 d	3–10 d	11–30 d	Total		
No vasospasm	84 (79%)	84 (68%)	55 (61%)	223 (70%)	0.02[b]	0.01[b]
Vasospasm present	22 (21%)	40 (32%)	35 (39%)	97 (30%)		
Total	106	124	90	320[c]		

[a] M/H, Mantel-Haenszel.
[b] Significance.
[c] No data for seven patients.

Procedural complications

Untoward events complicated 37 procedures (11.2%). The details and their clinical consequences are presented in *Table 6*. Procedure-related permanent morbidity affected eight patients (2.5%), and seven patients died (2.1%). Procedural complications were almost equally divided between ITT groups, with no statistically significant correlation between treatment timing and the incidence of complications ($P = 0.7$).

One patient underwent embolization of two aneurysms (internal carotid artery and middle cerebral artery aneurysms) and 3 days later bled twice because of rupture of an untreated aneurysm of the basilar tip, which in retrospect was probably the initially ruptured aneurysm. This event has not been included as a procedural complication.

Periprocedural clinical outcomes

The WFNS grades for patients before and 72 hours after endosaccular coil embolization are presented in *Table 7*. Before treatment, 70% of patients in Group 1 were in WFNS Grade 1 or 2, as were 78.4% of Group 2 and 83% of Group 3. Subtraction of the pretreatment WFNS grade from the posttreatment WFNS grade enabled us to identify patients who experienced deterioration during this period, either as a result of a procedural complication or as a consequence of the initial bleeding. The WFNS grade was either unchanged or improved 72 hours after the procedure for nearly the same proportion of patients in each ITT group (93.5% of Group 1, 89.5% of Group 2, and 91.5% of Group 3) (*Table 8*).

Twenty-eight patients (8.6%) experienced deterioration of at least one WFNS grade within 72 hours. This deterioration was attributable to a procedure-related complication for 15 patients, it was related to clinical vasospasm for 8 patients (7 patients in Group 2 and 1 patient in Group 1), it was related to hydrocephalus for 2 patients, and the cause was not identified for 3 patients (*Table 9*). There was therefore a higher incidence of deterioration unrelated to a procedural complication for Group 2, which presumably reflects an increased susceptibility to clinical vasospasm during this period (3–10 d after SAH). The numbers of patients are too small for statistical analysis.

The periprocedural outcomes (i.e., postprocedure WFNS grades) are presented in *Table 10*. There were more patients in good-grade condition (WFNS Grade 1 or 2) in the late-treatment group (ITT Group 3) both before (*Table 4*) and after EVT, but this was not statistically significant different from the other ITT groups ($P = 0.14$). These data suggest that the timing of the procedure after SAH did not significantly affect the short-term procedural outcomes.

TABLE 7. World Federation of Neurological Surgeons Grades for Patients Immediately before (Pretreatment), and 72 Hours after (Posttreatment) Endosaccular Coil Embolization[a]

WFNS Grade	No. of Patients	
	Pretreatment	Posttreatment
1	184 (56.3%)	172 (52.6%)
2	68 (20.8%)	65 (19.9%)
3	25 (7.6%)	27 (8.3%)
4	29 (8.9%)	37 (11.3%)
5	21 (6.4%)	26 (7.9%)

[a] **WFNS, World Federation of Neurological Surgeons.**

Clinical outcomes at 6 months

Sixteen patients (5%) died within 30 days after treatment, 9 patients as a result of procedure-related causes, 4 patients as a result of severe vasospasm, and 1 patient as a result of pulmonary embolism. Two patients died elsewhere, and the reasons are unknown.

Between 1 and 6 months after treatment, another seven patients died, four of whom were in poor neurological condition as a result of delayed complications of SAH; one patient died during an epileptic seizure, one died as a result of severe respiratory problems, and the cause of death was unknown for one patient. In total, 23 patients died during the 6-month follow-up period, and 5 additional patients were lost to follow-up monitoring.

Outcomes at 6 months, according to the MGOS, are presented in *Table 11*. Patients with MGOS scores of 1 or 2 (i.e., good outcomes) and MGOS scores of 3 to 5 (i.e., bad outcomes) were combined for the purpose of statistical analysis. Good outcomes were achieved for 81% of the patients in ITT Group 1, 84% in Group 2, and 80% in Group 3 (*Table 12*). No correlation between ITT and outcomes after 6 months was observed ($P = 0.79$). In other words, the data did not demonstrate that the timing of EVT influenced 6-month outcomes.

TABLE 6. Procedural Complications and Their Clinical Consequences

Procedural Complications	n[a]	No. of Patients			
		No Deficit	Temporary Deficit	Permanent Deficit	Death[b]
Aneurysm rupture	17 (5.2%)	5	6	3	3
Thromboemboli	8 (2.4%)	2	0	3	3
Coil herniation	6 (1.8%)	6	0	0	0
Parent artery occlusion	4 (1.2%)	1	0	2	1
Coil break	2 (0.6%)	2	0	0	0
Total	37 (11.2%)	16	6	8	7

[a] **n, number of patients (percentage of all patients).**
[b] **Death within the first week after treatment.**

TABLE 8. Changes in World Federation of Neurological Surgeons Grades 72 Hours after the Procedure[a]

	No. of Patients				P (χ^2)
	0–2 d	3–10 d	11–30 d	Total	
WFNS grade same/improved	100 (93.5%)	112 (89.5%)	87 (91.5%)	299[b] (91.4%)	0.577
WFNS grade deteriorated	7 (6.5%)	13 (10.5%)	8 (8.5%)	28 (8.6%)	

[a] WFNS, World Federation of Neurological Surgeons.
[b] Grade improved for nine patients.

TABLE 9. Causes of Deterioration in World Federation of Neurological Surgeons Grades within 72 Hours after Embolization

	No. of Patients		
	0–2 d	3–10 d	11–30 d
Procedural complications	6 (5.6%)	2 (1.6%)	7 (7.4%)
Nonprocedural complications	1 (0.9%)	11 (8.8%)	1 (0.9%)

Relationship between pretreatment WFNS grades and outcomes with different treatment times

Comparisons were made between 6-month outcomes and pretreatment WFNS grades according to the timing of EVT. For this analysis, patients in WFNS Grades 1 or 2 and WFNS Grades 3 to 5 and those with MGOS scores of 1 or 2 and MGOS scores of 3 to 5 were again combined (*Tables 13* and *14*). A χ^2 test comparing pretreatment WFNS grades and outcomes demonstrated a strong association ($P = 0.001$), with patients in good grades (pretreatment WFNS Grade 1 or 2) being more likely to experience good outcomes than those in poor grades (pretreatment WFNS Grade 3, 4, or 5). Ninety percent of patients in pretreatment WFNS Grade 1 or 2 experienced good outcomes, compared with only 58% of patients in pretreatment WFNS Grade 3, 4, or 5. This association was also apparent when investigated within each of the three ITT groups separately, and, although it was not significant for Group 3 patients (ITT of 11–30 d), the direction of the association was the same, i.e., patients in pretreatment WFNS Grades 1 and 2 were more likely to experience good outcomes.

Other effects on outcomes

Outcomes were similar for patients with aneurysms of either the anterior or posterior cerebral circulation; 83.0% of patients with anterior circulation aneurysms and 83.7% of patients with posterior circulation aneurysms achieved good outcomes (MGOS scores of 1 or 2). Furthermore, although a higher percentage of patients in good-grade condition (pretreatment WFNS Grade 1 or 2) and a lower incidence of angiographic vasospasm were observed among patients with posterior circulation aneurysms (both reached statistical significance), no association between aneurysm location and outcome at 6 months was observed, even after controlling for variables, i.e., pretreatment WFNS grade, angiographic vasospasm, and incidence of procedural complications.

There was a strong association between the presence of angiographic vasospasm and poor outcomes after 6 months ($P = 0.001$). Angiographic vasospasm was more common among patients who experienced rebleeding, occurring in 40.8% of such patients, compared with only 28.5% of patients who experienced only a single hemorrhaging episode.

Forty-nine patients experienced two or more episodes of hemorrhaging before EVT (*Table 4*). Among these patients, the pretreatment WFNS grades were good (WFNS Grade 1 or 2) for 31 patients and poor (WFNS Grade 3, 4, or 5) for 18 patients. Although the incidence of angiographic vasospasm and the proportion of patients in poor-grade condition (pretreatment WFNS Grades of 3–5) were higher for this subgroup ($P = 0.01$), no statistically significant correlation between this subgroup and worse outcomes at 6 months was observed ($P = 0.25$), even after controlling for both of these variables (pretreatment WFNS grade and angiographic vasospasm).

DISCUSSION

This report describes our experience with coil embolization for the treatment of 327 consecutive patients after aneurysmal SAH. The study does not demonstrate differences in 6-month outcomes when EVT was performed at different times after aneurysmal rupture. In other words, the day of treatment after SAH did not predict either a favorable or unfavorable outcome. This finding has implications for patient treatment but must be interpreted with care because of the difficulty of drawing firm conclusions from an observational study.

TABLE 10. Comparison of Posttreatment World Federation of Neurological Surgeons Grades (at 72 h) for the Three Interval-to-Treatment Groups[a]

WFNS Grade	No. of Patients				P (χ^2)
	0–2 d	3–10 d	11–30 d	Total	
1–2	71 (66%)	91 (73%)	75 (79%)	237 (72.5%)	0.14
3–5	36 (34%)	34 (27%)	20 (21%)	90 (27.5%)	

[a] WFNS, World Federation of Neurological Surgeons.

TABLE 11. Clinical Outcomes after 6 Months for the Three Interval-to-Treatment Groups[a]

MGOS Score	No. of Patients			
	0–2 d	3–10 d	11–30 d	Total
1	70 (21.5%)[b]	84 (25.7%)	64 (19.7%)	217 (66.9%)
2	17 (5.2%)	21 (6.5%)	12 (3.7%)	51 (15.4%)
3	7 (2.1%)	12 (3.6%)	6 (1.8%)	25 (7.5%)
4	3 (0.9%)	2 (0.6%)	1 (0.3%)	6 (1.8%)
5	10 (3.0%)	5 (1.5%)	8 (2.4%)	23 (6.9%)
No data	0	1 (0.3%)	4 (1.2%)	5 (1.5%)

[a] **MGOS, modified Glasgow Outcome Scale.**
[b] **Percentage of all patients.**

TABLE 12. Patient Outcomes, Pooled as Good (Modified Glasgow Outcome Scale Scores of 1 or 2) or Bad (Modified Glasgow Outcome Scale Scores of 3, 4, or 5) for Three Interval-to-Treatment Groups[a]

MGOS Score	No. of Patients				P (χ^2)
	0–2 d	3–10 d	11–30 d	Total	
1–2	87 (81%)	105 (84%)	76 (80%)	268 (82%)	0.79
3–5	20 (19%)	19 (15%)	15 (18%)	54 (17%)	
Total				322[b]	

[a] **MGOS, modified Glasgow Outcome Scale.**
[b] **Five patients were lost to follow-up monitoring.**

TABLE 13. Outcomes for Patients Treated in Good Clinical Conditions (Pretreatment World Federation of Neurological Surgeons Grade 1 or 2), According to Interval-to-Treatment Group[a]

	No. of Patients			
	0–2 d	3–10 d	11–30 d	Total
Good outcome	71 (95%)	89 (91%)	66 (86%)	226 (90%)
Bad outcome	4 (5%)	9 (9%)	11 (14%)	24 (10%)
Total	75	98	77	250

[a] **Good outcome, modified Glasgow Outcome Scale score of 1 or 2; bad outcome, modified Glasgow Outcome Scale score of 3, 4, or 5.**

TABLE 14. Outcomes for Patients Treated in Poor Clinical Conditions (Pretreatment World Federation of Neurological Surgeons Grade 3, 4, or 5), According to Interval-to-Treatment Group

	No. of Patients			
	0–2 d	3–10 d	11–30 d	Total
Good outcome	16 (50%)	16 (62%)	10 (71%)	42 (58%)
Bad outcome	16 (50%)	10 (38%)	4 (29%)	30 (42%)
Total	32	26	14	72

There are been many reports addressing the issue of the timing of aneurysm surgery after SAH (4, 12–14, 16, 17, 26, 27, 30). Chyatte et al. (4) reported that the incidence of vasospasm was affected by the timing of surgery and that patients who underwent surgery 0 to 3 days after SAH exhibited a higher incidence of postoperative ischemic symptoms, compared with patients who were surgically treated later. Similarly, Maurice-Williams and Kitchen (16) reported that early surgery was associated with higher mortality and morbidity rates than delayed surgery. However, a randomized study performed by Ohman and Heiskanen (21) suggested that there were benefits to operating early. Two hundred sixteen patients, of Hunt and Hess Grades I to III, were randomly allocated to undergo surgical clipping 0 to 3, 4 to 7, or 8 or more days after SAH, and outcomes were assessed at 3 months. Nine patients died as a result of rebleeding before clipping in the delayed-surgery groups, and the management morbidity rate was lowest, with a trend toward better outcomes, in the early (0–3 d)-surgery group, but this difference was not statistically significant.

The concept that ultra-early surgery was less likely to induce or coincide with symptoms of delayed ischemia attributable to vasospasm was supported by Taylor et al. (27), who reported on a series of 295 patients who were surgically treated before Day 5, between Days 6 and 10, or after Day 11. They observed (as a trend but not a statistically significant association) that surgery performed during the period of "maximal vulnerability" for delayed ischemia (6–10 d) synergistically worsened symptoms attributable to delayed ischemia. Furthermore, Solomon et al. (26) treated 145 selected patients by clipping within 7 days after SAH and observed that patients of Hunt and Hess Grades I or II who underwent surgery on Days 0 to 1 exhibited a significantly lower inci-

dence of symptoms attributable to delayed cerebral ischemia, compared with patients who underwent surgery on Days 4 to 7.

The International Cooperative Study on the Timing of Aneurysm Surgery (12, 13), which represents the largest study to date and provides the strongest evidence on which to base treatment decisions, demonstrated that late surgery was associated with better surgical results but 6-month outcomes were similar for patients treated early, because patients treated late experienced the consequences of aneurysmal rebleeding during the interval. It also demonstrated that rates of surgical complications were highest among patients who were surgically treated 4 to 10 days after SAH and that patients who underwent surgery on Days 7 to 10 after SAH experienced the least favorable outcomes and the highest mortality rates (13). Mikaoka et al. (17) compared mortality rates for patients treated before or after the fourth day after SAH. They also observed early surgical mortality rates to be highest but, when nonsurgical patients were included in the analysis, differences in mortality rates disappeared, except for patients in very poor-grade condition (Hunt and Hess Grade V). More recently, Whitfield et al. (30) reported a mixed retrospective (92 patients) and prospective (129 patients) study, analyzing two groups of patients who were treated either within 4 days or more than 4 days after SAH. They observed, in the prospective branch of the study, a tendency toward lower mortality rates and lower incidences of postoperative ischemia in the early-treatment group, and they suggested that such encouraging results could be achieved when surgery is combined with modern medical management, such as the prophylactic use of nimodipine and careful control of fluid balance. These studies have convinced many surgeons to adopt a policy of performing surgery before 4 days to prevent rebleeding and to postpone surgery for patients who present late or who are in poor clinical condition. The questions we have attempted to address are what the role of EVT is during the acute period after SAH and whether treatment should be similarly postponed, to avoid endovascular catheterization in the 4- to 10-day period.

Our finding that procedural morbidity and mortality rates were not affected by the timing of treatment challenges current surgical management. On the basis of the conclusions of the International Cooperative Study (12, 13), it is arguable that if rebleeding could be prevented and vasospasm effectively treated, craniotomy and clipping should be delayed. Coil embolization, which has been demonstrated to be effective in preventing early rebleeding (3, 15, 29), partly solves this therapeutic dilemma but may exacerbate vasospasm or introduce new threats to recovery. It is therefore pertinent to consider the potential effects of other factors that may affect outcomes after SAH.

The International Cooperative Study was a prospective, observational, epidemiological survey of surgical practice in the late 1980s. Patients were recruited after having been admitted to one of 68 participating centers within 3 days after SAH. They were not randomized for early or late surgery, but outcomes at 6 months were compared with those for patients treated by clipping at different times after SAH. We have chosen to analyze our data in a similar manner, but there are two fundamental differences in study methodologies; firstly, we collected data only for patients referred for EVT and, secondly, we assigned WFNS grades at the time of treatment, rather than at the time of admission to the hospital. Conclusions should therefore be based on the effects of timing on procedural morbidity rates and surgical outcomes, rather than overall management results, because undoubtedly some patients (for whom we have no data) were not referred because transfer was prevented by rebleeding or other complications, which would affect overall outcomes. Despite these limitations, we think it is useful to compare our results with those for patients treated surgically in the Cooperative Study, because that remains the largest single study of surgical practice.

That study was performed, and neurological assessments were made, before the introduction of WFNS grading and when aggressive medical management of vasospasm was not widely practiced. Patient assessments in the Cooperative Study were described in terms of neurological features, with 81% of patients being alert or drowsy, 76% having normal motor responses, and 75% having normal speech. Of the patients in the Cooperative Study, 75 to 80% were considered to be in good condition at admission, a rate comparable to that in our study, in which 77% of the patients were in WFNS Grades 1 or 2 before treatment.

The two series are comparable with respect to patient age and sex; in the Cooperative Study, the age range was 18 to 87 years (average, 50.4 yr) and the female/male ratio was 1.57:1. The sizes of the treated aneurysms were small ($<$11 mm) in 78% and 71.8%, large (11–24 mm) in 20% and 27.2%, and giant ($>$24 mm) in 2% and 0.9% of the cases in our study and the Cooperative Study, respectively. In our study, there were significantly more posterior circulation aneurysms, i.e., 28.5%, compared with only 8% in the Cooperative Study, reflecting a referral bias for EVT. Only the last feature is likely to affect the periprocedural morbidity rate, because posterior circulation aneurysms were associated with the highest surgical mortality rate in the Cooperative Study.

The incidence of angiographic vasospasm at the time of treatment in our series was 30.5% overall and, as in the Cooperative Study, its frequency increased with time after SAH. In the Cooperative Study, angiograms indicated vasospasm for only 4.5% of patients on Day 0 and vasospasm was more frequent on each subsequent day until Day 7 (the last day studied), when the incidence reached 32%. In our series, angiographic vasospasm was most common (39%) in angiograms obtained after Day 11, although the WFNS grades of these patients were slightly better than those in the other groups. This observation seems paradoxical, because poor pretreatment WFNS grade and angiographic vasospasm were statistically correlated (patients with angiographic vasospasm were more likely in WFNS Grades 3, 4, or 5 before treatment, $P = 0.001$), but the finding may be explained by the known variability in the clinical expression of vasospasm and the fact that angiographic vasospasm may persist for weeks after onset (6) and would therefore be evident in late angiograms. Reassuringly, both variables (pretreatment WFNS grade and

angiographic vasospasm) exhibited similar correlations with 6-months outcome in the two studies.

However, we also recorded a higher incidence of angiographic vasospasm (21.7%), compared with the Cooperative Study, in the acute period (Days 0–2). This reflects a fundamental difference in study methodologies. Because patients were treated by EVT as soon as possible after admission, rebleeding did not occur more frequently among patients undergoing late EVT. In fact, patients who survived rebleeding were frequently referred for urgent EVT and were therefore treated in the early-ITT group. Nonsurvivors were obviously not referred. Therefore, because of our treatment policy, rebleeding before EVT and angiographic vasospasm were most common among patients in Group 1.

Patients who experienced more than one episode of hemorrhaging, i.e., rebleeding before embolization, were in poorer clinical condition than were those treated after a single ictus. Of such patients, 43% were treated within 2 days after the last hemorrhaging episode, which contributed to the relatively higher percentage of patients in poor grades in ITT Group 1. It is difficult to identify the likely effect of such bias on procedural morbidity rates. However, because the majority of patients are likely to exhibit improvement between admission (the point at which clinical grade classifications were historically performed) and surgery and because the admission grades in the Cooperative Study and the pretreatment grades in this study are compatible, any bias caused by the different times at which pretreatment assessments were performed would tend to disadvantage EVT. However, the clinical condition at admission has been clearly related to outcomes after SAH (13) and represents the benchmark against which treatment efficacy has been assessed. For this reason and because of the ascertainment difficulty discussed above, it is unwise to draw firm conclusions from our data regarding the timing of EVT and 6-month outcomes. Such a comparison will require data from controlled randomized studies, such as the International Subarachnoid Aneurysm Trial, which tests concurrent management strategies, including the efficacy of adjuvant therapies such as angioplasty. In the International Subarachnoid Aneurysm Trial, patients are randomly allocated to undergo clipping or EVT after intra-arterial angiography, but the timing of treatment is not prescribed. To date, only one small controlled study of 109 patients treated by clipping or EVT has been reported; that study observed outcomes to be comparable (28). It is unlikely that a study that randomly allocates patients to direct aneurysm treatment at different times after SAH will ever be repeated.

The theoretical advantage of the endovascular approach is that it allows early intervention and thus protection from rebleeding. This study demonstrates that treatment-related morbidity rates are less dependent on timing than are rates for conventional surgery. Angiographic vasospasm rarely prevented early treatment; during the study period, EVT failed because of difficulty in accessing aneurysms, because of vasospasm or tortuous vessels, for only three patients. The outcomes for our patients suggest that occlusion of ruptured aneurysms by endovascular coil packing should be performed regardless of the interval after SAH. However, although this result supports our treatment strategy, the strategy included postponement of treatment if the condition of the patient was too unstable for safe anesthesia. With this caveat, it follows that, if EVT can be undertaken at any time after SAH without increasing the procedural morbidity and mortality rates or having an adverse effect on late outcomes, then patients who miss the 48-hour time window for early surgery should be referred for EVT, rather than waiting for delayed surgery. The present study is the first of which we are aware to address this issue, and it suggests that patients can and should be treated with EVT as soon as possible, irrespective of the interval between bleeding and arrival at the hospital.

ACKNOWLEDGMENTS

We thank Vanessa Ramraj for typing the manuscript and the radiographers and nurses of the Department of Neuroradiology at the Radcliffe Infirmary for their expert assistance, as well as the many neurosurgeons who referred their patients for EVT.

Received, December 31, 1999.
Accepted, August 4, 2000.
Reprint requests: James V. Byrne, F.R.C.S., F.R.C.R., Department of Radiology, The Radcliffe Infirmary NHS Trust, Woodstock Road, Oxford, England OX2 6HE. Email: james.byrne@radiology.ox.ac.uk

REFERENCES

1. Auere LM: Unfavourable outcome following early surgical repair of ruptured cerebral aneurysms: A critical review of 238 patients. **Surg Neurol** 35:152–158, 1991.
2. Byrne JV, Adams CBT, Kerr RSC, Molyneux AJ: Endosaccular treatment of inoperable intracranial aneurysms with platinum coils. **Br J Neurosurg** 9:585–592, 1995.
3. Byrne JV, Molyneux AJ, Brennan RP, Renowden SA: Embolisation of recently ruptured intracranial aneurysms. **J Neurol Neurosurg Psychiatry** 59:616–620, 1995.
4. Chyatte D, Fode NC, Sundt TM Jr: Early versus late intracranial aneurysm surgery in subarachnoid hemorrhage. **J Neurosurg** 69:326–331, 1988.
5. Cognard C, Weill A, Castaings L, Rey A, Moret J: Intracranial berry aneurysms: Angiographic and clinical results after endovascular treatment. **Radiology** 206:499–510, 1998.
6. Du Boulay GH, Marshall J, Merory J, Symon L: The location of spasm and its relation to symptoms, in Wilkins RH (ed): *Cerebral Arterial Spasm*. Baltimore, Williams & Wilkins, 1980, pp 394–396.
7. Edner G, Kågström E, Wallstedt L: Total overall management and surgical outcome after aneurysmal subarachnoid haemorrhage in a defined population. **Br J Neurosurg** 6:409–420, 1992.
8. Graves V, Strother C, Duff T, Perl J II: Early treatment of ruptured aneurysms with Guglielmi detachable coils: Effects on subsequent bleeding. **Neurosurgery** 37:640–648, 1995.
9. Gruber A, Ungersbock K, Reinprecht A, Czech T, Gross C, Bednar M, Richling B: Evaluation of cerebral vasospasm after early surgical and endovascular treatment of ruptured intracranial aneurysms. **Neurosurgery** 42:258–268, 1998.
10. Guglielmi G, Viñuela F, Dion J, Duckwiler G: Electrothrombosis of saccular aneurysms via endovascular approach: Part II—Preliminary clinical experience. **J Neurosurg** 75:8–14, 1991.

11. Jennett B, Bond M: Assessment of outcome after severe brain damage: A practical scale. **Lancet** 1:480–484, 1975.
12. Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP, Kongable GL: The International Cooperative Study on the Timing of Aneurysm Surgery: Part 1—Overall management results. **J Neurosurg** 73:18–36, 1990.
13. Kassell NF, Torner JC, Jane JA, Haley EC Jr, Adams HP: The International Cooperative Study on the Timing of Aneurysm Surgery: Part 2—Surgical results. **J Neurosurg** 73:37–47, 1990.
14. Le Roux PD, Elliot JP, Newell DW, Grady MS, Winn HR: The incidence of surgical complications is similar in good and poor grade patients undergoing repair of ruptured anterior circulation aneurysms: A retrospective review of 355 patients. **Neurosurgery** 38:887–895, 1996.
15. Malisch T, Guglielmi G, Viñuela F, Duckwiler G, Gobin YP, Martin NA, Frazee JG: Intracranial aneurysms treated with the Guglielmi detachable coil: Midterm clinical results in 100 consecutive patients. **J Neurosurg** 87:176–183, 1997.
16. Maurice-Williams RS, Kitchen ND: Ruptured intracranial aneurysms: Learning from experience. **Br J Neurosurg** 8:519–527, 1994.
17. Mikaoka M, Sato K, Ishii S: A clinical study of the relationship of timing to outcome of surgery for ruptured cerebral aneurysm. **J Neurosurg** 79:373–378, 1993.
18. Molyneux A, Kerr R: Endovascular aneurysm treatment and the incidence of vasospasm. **AJNR Am J Neuroradiol** 20:944–945, 1999 (letter).
19. Moret J, Pierot L, Boulin A, Castaings L, Rey A: Endovascular treatment of anterior communicating artery aneurysms using Guglielmi detachable coils. **Neuroradiology** 38:800–805, 1996.
20. Murayama Y, Malisch T, Guglielmi G, Mawad ME, Viñuela F, Duckwiler GR, Gobin YP, Klucznick RP, Martin NA, Frazee J: Incidence of cerebral vasospasm after endovascular treatment of acutely ruptured aneurysms: Report of 69 cases. **J Neurosurg** 87:830–835, 1997.
21. Ohman J, Heiskanen O: Timing of operation for ruptured supratentorial aneurysms: A prospective randomized study. **J Neurosurg** 70:55–60, 1989.
22. Proust F, Hannequin D, Langlois O, Freger P, Creissard P: Causes of morbidity and mortality after ruptured aneurysm surgery in a series of 230 patients: The importance of control angiography. **Stroke** 26:1553–1557, 1995.
23. Raymond J, Roy D, Bojanowski M, Moumdjian R, L'Esperance G: Endovascular treatment of acutely ruptured and unruptured aneurysms of the basilar bifurcation. **J Neurosurg** 86:211–219, 1997.
24. Rowe JG, Byrne JV, Molyneux A, Rajagopalan B: Haemodynamic consequences of embolizing aneurysms: A transcranial Doppler study. **Br J Neurosurg** 9:749–757, 1995.
25. Säveland H, Hillman J, Brandt L, Edner G, Jakobsson KE, Algers G: Overall outcome in aneurysmal subarachnoid hemorrhage: A prospective study from neurosurgical units in Sweden during a 1-year period. **J Neurosurg** 76:729–734, 1992.
26. Solomon RA, Onesti ST, Klebanoff L: Relationship between the timing of aneurysm surgery and the development of delayed cerebral ischemia. **J Neurosurg** 75:56–61, 1991.
27. Taylor B, Harries P, Bullock R: Factors affecting outcome after surgery for intracranial aneurysm in Glasgow. **Br J Neurosurg** 5:591–600, 1991.
28. Vanninen R, Koivisto T, Saari T, Hernesniemi J, Vapalahti M: Ruptured intracranial aneurysms: Acute endovascular treatment with electrolytically detachable coils—A prospective randomized study. **Radiology** 211:325–336, 1999.
29. Viñuela F, Duckwiler G, Mawad M: Guglielmi detachable coil embolization of acute intracranial aneurysm: Perioperative anatomical and clinical outcome in 403 patients. **J Neurosurg** 86:475–482, 1997.
30. Whitfield PC, Moss H, O'Hare D, Smielewski P, Pickard JD, Kirkpatrick PJ: An audit of aneurysmal subarachnoid haemorrhage: Earlier resuscitation and surgery reduces patient stay and deaths from rebleeding. **J Neurol Neurosurg Psychiatry** 60:301–306, 1996.
31. World Federation of Neurological Surgeons Committee: Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. **J Neurosurg** 68: 985–986, 1988.
32. Yalamanchili K, Rosenwasser RH, Thomas JE, Liebman K, McMorrow C, Gannon P: Frequency of cerebral vasospasm in patients treated with endovascular occlusion of intracranial aneurysms. **AJNR Am J Neuroradiol** 19:553–558, 1998.

COMMENTS

Surgery during the first 7 to 10 days after subarachnoid hemorrhage (SAH) was initially considered dangerous. The fact that so many of the 327 patients in the present series were admitted 1 week or more after SAH is rather exceptional now and differs from the policy of many institutions that treat ruptured aneurysms. I think there should be a discussion of why so many patients arrived so late. The 327 patients studied represent a highly selected group of patients with aneurysms, with some referral biases. In addition to an extreme overrepresentation of posterior circulation aneurysms (1), there seems to be a selection of the patients accepted for treatment. The fact that the number of rebleeding episodes was less for those treated late might also be attributable to the fact that some patients with rebleeding died before referral.

In this series, one-half of the patients were treated with coils, but there are no clear criteria regarding which patients were surgically treated and which were treated with coils. It is our experience, in a country without referral biases, that less than one-half of ruptured cerebral aneurysms can be treated with coils.

Patients in Grade 5 should be treated separately, because their outcomes are quite different from those in Grades 3 and 4. Patients who are in Grade 5 several days after SAH seldom make useful recoveries and consequently seldom benefit from surgical treatment (2–5). I recommend (although it may already have been performed) that the outcomes of the cases should be analyzed day by day, to determine eventual "weak" days, i.e., days with increased numbers of complications or poor outcomes. In our experience, Days 4 to 7 proved to be very hazardous, but this was explained by the poor condition of the patients who were treated after delays of some days. In other words, patients in poor condition or with difficult aneurysms tend to be surgically treated later in surgical series. In this series, did these factors have an effect?

It is interesting that the authors of this article come to the same conclusion that we reached almost 10 years ago, when analyzing our series of early open surgery (2–4). The timing of surgery had little influence on outcomes, which were predominantly affected by the preoperative grade. The preoperative grade was of major importance for patients who were surgi-

cally treated early; postoperative ischemia played an important role in the outcomes of patients who were surgically treated later.

I recommend immediate surgery for patients who are in Hunt and Hess Grades 1 to 4 or exhibiting improvement in Grade 5. It is clear that only patients whose aneurysms do not present a particular technical difficulty for the operating neurosurgeon, because of size, configuration, direction, or location, should be surgically treated. Patients whose lives seem to be in jeopardy because of recurrent hemorrhaging require especially urgent treatment, as do those with intracerebral clots or severe hydrocephalus. It is clear that, with this policy, the surgical mortality rate will increase. Immediate/early aneurysm surgery is a heavy burden for neurosurgeons, because of the higher mortality and complication rates for acutely ill patients. However, the management outcome, i.e., the number of patients surviving to independent lives, should improve (2). Referring the care of some challenging lesions (vertebrobasilar, proximal carotid artery, nonsaccular, and large to giant aneurysms) to a few experienced surgeons with adequate surgical experience remains a factor for improved patient outcomes.

The results of endovascular treatment (EVT) in this series are good and challenge traditional surgery. Those who continue to ligate the aneurysm neck with open surgery must do so with minimal or no retraction or manipulation of the brain (like endovascular surgeons), gentle handling and saving of all (even the smallest) arteries and veins, and perfect clipping of the aneurysm. Urgent early endovascular wire coiling of the dome of the ruptured sac can be used in selected cases to protect the patient during the period of fresh SAH and vasospasm, so that a definitive operation can be performed later, after brain healing. In selected cases with small-necked aneurysms, no open corrective surgery seems to be necessary (7).

Despite improvements in surgical and endovascular techniques, we are far from achieving ideal results. Because there are now methods to detect aneurysms before they rupture, there is progress toward the best timing for aneurysm surgery, i.e., before rupture. This will improve the management results more than any new technical innovation (6).

Juha Hernesniemi
Helsinki, Finland

1. Drake CG, Peerless SJ, Hernesniemi JA: *Surgery of Vertebrobasilar Aneurysms: London, Ontario, Experience in 1767 Patients.* Vienna, Springer-Verlag, 1996.
2. Fogelholm R, Hernesniemi J, Vapalahti M: Impact of early surgery on outcome after aneurysmal subarachnoid hemorrhage: A population-based study. **Stroke** 24:1649–1654, 1993.
3. Hernesniemi J, Vapalahti M, Niskanen M, Tapaninaho A, Kari A, Luukkonen M, Puranen M, Saari T, Rajpar M: One-year outcome in early aneurysm surgery: A 14 years experience. **Acta Neurochir (Wien)** 122:1–10, 1993.
4. Niskanen M, Hernesniemi J, Vapalahti M, Kari A: One-year outcome in early aneurysm surgery: Prediction of outcome. **Acta Neurochir (Wien)** 123:25–32, 1993.
5. Peerless SJ, Hernesniemi JA, Gutman FB, Drake CG: Early surgery for ruptured posterior circulation aneurysms. **J Neurosurg** 80: 653–649, 1994.
6. Ronkainen A, Hernesniemi J, Puranen M, Niemitukia L, Vanninen R, Ryynänen M, Kuivaniemi H, Tromp G: Familial intracranial aneurysms. **Lancet** 349:380–384, 1997.
7. Vanninen R, Koivisto T, Saari T, Hernesniemi J, Vapalahti M: Ruptured intracranial aneurysms: Acute endovascular treatment with electrolytically detachable coils—A prospective randomized study. **Radiology** 211:325–336, 1999.

This article evaluates the timing of treatment of ruptured aneurysms by EVT. The authors examined 327 consecutive patients treated by coiling within 30 days after acute SAH. Outcomes were assessed by comparing immediate pretreatment World Federation of Neurological Surgeons grades, 72-hour posttreatment World Federation of Neurological Surgeons grades, and modified Glasgow Outcome Scale scores at 6 months.

The authors concluded that the timing of EVT after acute bleeding did not affect periprocedural morbidity rates or 6-month outcomes. On the basis of this single-institution study, they further concluded that patients who are not surgically treated within 48 hours after acute hemorrhaging should be referred for EVT to treat their aneurysms, because it may protect patients from further rebleeding, and that surgery between 3 and 10 days is associated with significantly higher surgical morbidity rates than those for EVT.

The authors represent a tertiary referral center for intracranial aneurysm therapy. That center is the core laboratory for the International Subarachnoid Aneurysm Trial, which is a prospective randomized study comparing surgical clipping with EVT for acutely ruptured aneurysms. That study, when completed, will certainly be the largest prospective trial to evaluate the efficacy of EVT of aneurysms, in terms of safety, efficacy, and patient outcomes, compared with conventional surgical clipping.

The vascular neurosurgical and endovascular surgical communities await the final results from the International Subarachnoid Aneurysm Trial, to confirm the aforementioned findings. It is necessary not only to review the 6-month clinical follow-up results but also to evaluate 1- and 2-year follow-up results for EVT, because EVT may not lead to complete aneurysm obliteration in a certain percentage of cases, particularly large and giant cerebral aneurysms with wide angiographic necks. Therefore, although assessment at 6 months may indeed demonstrate short-term efficacy and improved clinical outcomes with endovascular interventions, we should also critically evaluate long-term efficacy and clinical outcomes for this treatment modality.

Randall T. Higashida
Interventional Neuroradiologist
San Francisco, California

Baltsavias et al. address a very interesting, sufficiently focused topic in this study, by analyzing the results for an impressively large group of patients. The authors performed this large organized study in a way that allows accurate

comparison with the International Cooperative Study on the Timing of Aneurysm Surgery. The International Cooperative Study suggested that surgery during the time of greatest risk for vasospasm worsened outcomes. The main question addressed by Baltsavias et al. is whether the timing of EVT has the same effect on outcomes as does that of craniotomy. Before we can evaluate the results of the study, we must analyze the potential biases in the study groups.

The study design included nonrandomized noncontrolled patient entry. Although the authors cannot be faulted for this, because every patient was treated as soon as reasonably possible after referral, it does introduce potential differences between the study groups. Specifically, age, clinical grade, and angiographic vasospasm were different for the late-treatment group, compared with the other groups. The authors correctly contend that improvement in clinical grades may simply represent the natural course after SAH. Conversely, the late-treatment group was, on average, older, with greater angiographic evidence of vasospasm at presentation. Despite the authors' contention that age was not correlated with outcomes and therefore did not bias their study, each of these variables has been correlated with worsened outcomes by other authors. Collectively, these differences would be expected to result in worsened outcomes for the delayed-treatment group in this study. The fact that no differences were noted between treatment groups supports the reliability of the results.

The periprocedural results and outcomes were very interesting. Although no significant differences were observed between groups with respect to the incidence of procedural complications or worsening of World Federation of Neurological Surgeons grades, clinical deterioration for reasons other than procedural complications was much more likely in the intermediate (3–10 d)-treatment group. Was this difference a result of greater patient susceptibility to injury during this time period, as suggested by the Cooperative Study? Or was this merely a reflection of the onset of vasospasm in a subset of patients who would have exhibited the same risk of deterioration with or without treatment? We do not know the proportions of patients in the early- and late-treatment groups who exhibited deterioration between Days 3 and 10 because of vasospasm. Therefore, we cannot precisely determine the reason for the difference in short-term outcomes.

The final result, however, is that the authors observed no differences in 6-month outcomes. Unlike the results of craniotomies in the Cooperative Study, EVT performed during the period of highest risk for vasospasm did not adversely affect outcomes. The implications are intriguing. The cause of worsened outcomes with surgery performed between Days 7 and 10 in the Cooperative Study is debatable. Some authors contend that arteries exposed to SAH are more likely to spasm if they are subsequently manipulated externally. Others suggest that the brain is simply more susceptible to ischemic insult during this period and, therefore, tolerates exposure and retraction during craniotomy less well than at other times. Whatever the mechanism, EVT does not seem to trigger the same reaction as craniotomy. This study thus joins a growing body of evidence that suggests that EVT for intracranial aneurysms is associated with less morbidity than is craniotomy. The greater durability of clip ligation, compared with coil embolization, remains the sole advantage of craniotomy. If endovascular techniques that match the durable results of clip ligation are developed, EVT will become the clear treatment of choice for intracranial aneurysms.

Andrew J. Ringer
L. Nelson Hopkins
Buffalo, New York

Baltsavias et al. describe their experience with 327 patients with aneurysms who were treated by endovascular coil embolization within 30 days after their last episode of bleeding. Only 33% of the patients, however, were treated within 48 hours, and there were two additional groups, with Group 2 (38%) being treated between Days 3 and 10 and Group 3 (29%) being treated between Days 11 and 30. The point that the authors make is that, unlike in the Cooperative Study for the Timing of Aneurysm Surgery, there were no differences in morbidity or mortality rates for patients treated early or late or during the period of symptomatic and angiographic vasospasm.

I think that many surgical groups, and particularly the Seattle group, have reported that, even in the presence of severe vasospasm, craniotomies to secure the aneurysms, followed by immediate angioplasty, represent a reasonable alternative. We reported a possible decreased incidence of spasm among patients who were treated with endosacular occlusion, and this decrease may have contributed to the findings for the patient population described by the authors. Also, almost two-thirds of the patients were admitted and treated between Day 3 and Day 30, and these patients were preselected to progress well, i.e., they survived until transfer could be arranged. It is unclear how many patients in the entire group died at the referring institution, as a result of either vasospasm or rebleeding, before transfer.

Robert H. Rosenwasser
Philadelphia, Pennsylvania