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Does Treatment of Ruptured Intracranial Aneurysms Within 24 Hours Improve Clinical Outcome?

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Background and Purpose—The purpose of this study was to analyze whether treating ruptured intracranial aneurysms within 24 hours of subarachnoid hemorrhage improves clinical outcome.

Methods—An 11-year database of consecutive ruptured intracranial aneurysms treated with endovascular coiling or craniotomy and clipping was analyzed. Outcome was measured by the modified Rankin Scale at 6 months. Our policy is to treat all cases within 24 hours of subarachnoid hemorrhage. Treatment delays are due to nonclinical logistical factors.

Results—Two hundred thirty cases were coiled or clipped within 24 hours of subarachnoid hemorrhage and 229 at >24 hours. No difference in age, gender, smoking, family history of subarachnoid hemorrhage, aneurysm size, or aneurysm location was found between the groups. Poor World Federation of Neurological Surgeons clinical grade patients were overrepresented in the ultra-early group. Increasing age and higher World Federation of Neurological Surgeons clinical grade were predictors of poor outcome. Eight point zero percent of cases treated within 24 hours of subarachnoid hemorrhage (ultra-early) were dependent or dead at 6 months compared with 14.4% of those treated at >24 hours (delayed), a 44.0% relative risk reduction and a 6.4% absolute risk reduction (χ^2, P=0.044). A total of 3.5% of cases coiled within 24 hours were dependent or dead at 6 months compared with 12.5% of cases coiled at 1 to 3 days, an 82% relative risk reduction and a 10.2% absolute risk reduction (χ^2, P=0.040). These groups did not differ in age, World Federation of Neurological Surgeons clinical grade, aneurysm size, or aneurysm location.

Conclusions—Treatment of ruptured aneurysms within 24 hours is associated with improved clinical outcomes compared with treatment at >24 hours. The benefit is more pronounced for coiling than clipping. **(*Stroke*. 2011;42:1936-1945.)**

Key Words: angiography ■ endovascular treatment ■ interventional neuroradiology ■ intracranial aneurysm ■ neurosurgery ■ outcome ■ subarachnoid hemorrhage ■ timing

The timing of definitive management of acutely ruptured intracranial aneurysms (endovascular coiling or craniotomy and clipping) has been the subject of considerable debate. Earlier treatment of the ruptured aneurysm lowers the incidence of rebleeding but was historically regarded as a higher risk than a delayed procedure.[1–11]

The literature to date on treatment timing has debated and documented the shift from advocacy of late surgery, defined as >10 days postsubarachnoid hemorrhage (SAH), to "early" surgery, defined as 1 to 3 days post-SAH. Studies analyzing so-called "ultra-early" aneurysm treatment, within 24 hours of SAH, are few in number. To date no published data exist that directly compares ultra-early treatment (within 24 hours of aneurysmal SAH) with treatment at >24 hours post-SAH.[2,7,12–28]

We believe that coiling or clipping of ruptured aneurysms within 24 hours of aneurysmal SAH (ultra-early) is associated with improved clinical outcome compared with coiling or clipping at >24 hours after SAH. We undertook a prospective audit of outcomes to investigate this.

Materials and Methods

A database of all ruptured intracranial aneurysms treated with endovascular coiling or craniotomy and clipping was maintained prospectively at a quaternary referral center for aneurysm treatment over an 11-year period (1997 to 2007). The database was retrospectively updated with long-term clinical outcome data. Data analysis was performed using statistical analysis software (IBM PASW/SPSS Version 18.0). Pearson χ^2, Student t test, Mantel-Haenszel test for linear association, and logistical regression were used where appropriate.

Inclusion/Exclusion Criteria and Data Collection

Only cases of proven aneurysmal SAH were included. Consecutive cases of coiling or clipping of acutely ruptured aneurysms were entered prospectively into a database. Cases of SAH due to arterial dissection, trauma, arteriovenous malformation rupture, perimesencephalic venous hemorrhage, or unknown etiology were excluded. Patients who died in the first 24 hours before treatment were also excluded. Of the 563 cases that met the prospective inclusion criteria, 104 of these were lost to follow-up and are excluded from this study because the end point is clinical outcome at 6 months. The series represents 459 cases of aneurysmal SAH treated with coiling or clipping.

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Table 1. Patient Demographics, Case Characteristics, Treatment Modality, and 6-Month Outcome: Comparison of Ultra-Early Treatment (Within 24 Hours of SAH) and Delayed Treatment (>24 Hours After SAH)*

	All Cases		Treatment Timing: Ultra-Early Treated at <24 h		Treatment Timing: Delayed Treated at >24 h			Statistical Test (Ultra-Early vs Delayed)
	Mean (SD)	n (row %)	Mean (SD)	n (row %)	Mean (SD)	n (row %)	*P*	Test Used
Total no. of cases		459		230		229		
Age on admission, y	53 (14.4)		52 (13.0)		54 (15.6)		0.129	Independent *t* test
Gender								
Female		297 (65%)		153 (52%)		144 (48%)	0.415	Pearson χ^2
Male		162 (35%)		77 (48%)		85 (52%)		
		459		230 (50%)		229 (50%)		
Smoking status								
Smoker		100 (22%)		53 (53%)		47 (47%)	0.497	Pearson χ^2
Nonsmoker		354 (78%)		174 (49%)		180 (51%)		
		454		227 (50%)		227 (50%)		
FHx SAH								
FHx of SAH		11 (2%)		5 (45%)		6 (55%)	0.760	Pearson χ^2
No FHx of SAH		443 (98%)		222 (50%)		221 (50%)		
		454		227 (50%)		227 (50%)		
WFNS clinical grade								
1		181 (40%)		83 (46%)		98 (54%)	0.029	Mantel-Haenszel
2		123 (27%)		58 (47%)		65 (53%)		
3		50 (11%)		27 (54%)		23 (46%)		
4		52 (11%)		33 (63%)		19 (37%)		
5		52 (11%)		29 (56%)		23 (44%)		
		458		230 (50%)		228 (50%)		
WFNS dichotomized								
WFNS 1–3		354 (77%)		168 (47%)		186 (53%)	0.029	Pearson χ^2
WFNS 4–5		104 (23%)		62 (60%)		42 (40%)		
		458						
Fisher grade								
1		27 (11%)		8 (30%)		19 (70%)	0.011	Pearson χ^2
2		36 (15%)		12 (33%)		24 (67%)		
3		68 (28%)		38 (56%)		30 (44%)		
4		112 (46%)		63 (56%)		49 (44%)		
		243		121 (50%)		122 (50%)		
Fisher grade dichotomized								
Fisher 1 and 2		63 (26%)		20 (32%)		43 (68%)	0.001	Pearson χ^2
Fisher 3 and 4		180 (74%)		101 (56%)		79 (44%)		
Aneurysm size, mm	6.8 (3.8)		6.9 (3.7)		6.8 (4.0)		0.883	Independent variables *t* test
Aneurysm location								
Posterior circulation		66 (14%)		39 (59%)		27 (41%)	0.192	Pearson χ^2
ICA, ACA, AComA		302 (66%)		143 (47%)		159 (53%)		
MCA		91 (20%)		48 (53%)		43 (47%)		
		459		230 (50%)		229 (50%)		
Aneurysm location dichotomized								
Anterior circulation		393 (86%)		191 (49%)		202 (51%)	0.115	Pearson χ^2
Posterior circulation		66 (14%)		39 (59%)		27 (41%)		
		459		230 (50%)		229 (50%)		

(*Continued*)

Table 1. Continued

	All Cases		Treatment Timing: Ultra-Early Treated at <24 h		Treatment Timing: Delayed Treated at >24 h			Statistical Test (Ultra-Early vs Delayed)
	Mean (SD)	n (row %)	Mean (SD)	n (row %)	Mean (SD)	n (row %)	*P*	Test Used
Treatment method								
Clipped		291 (63%)		128 (44%)		163 (56%)	0.001	Pearson χ^2
Coiled		168 (37%)		102 (61%)		66 (39%)		
		459		230 (50%)		229 (50%)		
Timing category								
Ultra-early (<24 h)		230 (50%)		230 (100%)		0 (%)		
"Early" (24–72 h)		202 (44%)		0 (%)		202 (88%)		
Intermediate (3–10 d)		18 (4%)		0 (%)		18 (8%)		
Late (>10 d)		9 (2%)		0 (%)		9 (4%)		
		459		230		229		
mRS at 6 mo		n (column %)		n (column %)		n (column %)		
0		205 (50%)		112 (56%)		93 (44%)	0.024	Mantel-Haenszel
1		140 (34%)		61 (31%)		79 (38%)		
2		17 (4%)		10 (5%)		7 (3%)		
3		9 (2%)		3 (2%)		6 (3%)		
4		10 (2%)		4 (2%)		6 (3%)		
5		4 (1%)		1 (1%)		3 (1%)		
6		23 (6%)		8 (4%)		15 (7%)		
		408		199		209		
Clinical outcome at 6 mo (mRS dichotomized)		n (column %)		n (column %)		n (column %)		
Independence (mRS 0–2)		362 (89%)		183 (92%)		179 (86%)	0.044	Pearson χ^2
Death or dependence (mRS 3–6)		46 (11%)		16 (8%)		30 (14%)		
		408		199		209		

SAH indicates subarachnnoid hemorrhage; FHx, family history; WFNS, World Federation of Neurological Societies; ICA, internal carotid artery; ACA, anterior cerebral artery; AComA, anterior communicating artery; MCA, middle cerebral artery; mRS, modified Rankin Scale.

*The results are grouped into ultra-early (treated at <24 h) and not ultra-early (treated at >24 h). The right-hand columns are the results of the relevant statistical tests applied to the difference between the groups.

Patent demographics, smoking status, and family history of SAH were recorded. Admission World Federation of Neurological Surgeons (WFNS) clinical grade was recorded for all except 1 case.[29] Aneurysm anatomic location and maximal size were recorded for all cases. The time between SAH ictus and coiling or clipping was recorded; the ictus defined the onset of headache or collapse. Clinical outcomes were measured at ≥6 months using the patient questionnaire-based modified Rankin Scale (mRS) system.[30] These outcome data are available for 408 of the 459 cases. A dichotomized mRS published in other aneurysm trials is also used as an outcome measure. mRS scores 0, 1, and 2 are grouped into "independence" and mRS scores 3, 4, 5, and 6 are grouped into "dependence or death."

Missing Data

Missing data are an inherent problem in a longitudinal retrospective study. This institution is a quaternary referral center, and many cases are followed up by the hospitals that they initially presented to. Of the cases that were lost to follow-up or where the outcome data are incomplete, no statistically significant difference was observed in treatment timing (χ^2, $P=0.313$).

Clinical Methods

SAH was diagnosed either by brain CT or lumbar puncture and cerebrospinal fluid analysis. Intracranial aneurysms were diagnosed by catheter digital subtraction angiography or CT angiography. The use of diagnostic imaging evolved over the study period with the advent of CT angiography as a first-line imaging tool. In almost all cases, a catheter digital subtraction angiogram was also performed with a small minority of ruptured aneurysms being transferred to the operating room on the basis of CT angiography findings alone. A few cases of unexpected aneurysmal SAH were diagnosed on MRI; these patients all underwent subsequent digital subtraction angiography.

The policy of the cerebrovascular neurosurgeons and the neurointerventionists in this institution is to treat ruptured aneurysms, regardless of age or clinical grade, within 24 hours of the SAH ictus (ultra-early). The cases in which ruptured aneurysms were not coiled or clipped within 24 hours do not represent a clinical decision to delay treatment. The delays were due variably to transfer from other hospitals, remote transfers from rural areas or interstate, internal hospital logistical delays (access to operating rooms, anesthetic and nursing staff), and late diagnoses.

A decision was jointly made on a case-by-case basis by the on-call neurointerventional radiologist and the on-call neurosurgeon as to the best treatment modality. This data series spans the sentinel International Subarachnoid Aneurysm Trial publications that demonstrated that coiling offers better clinical outcomes for aneurysms judged to be equally suited to both modalities.[31–34] The proportion of

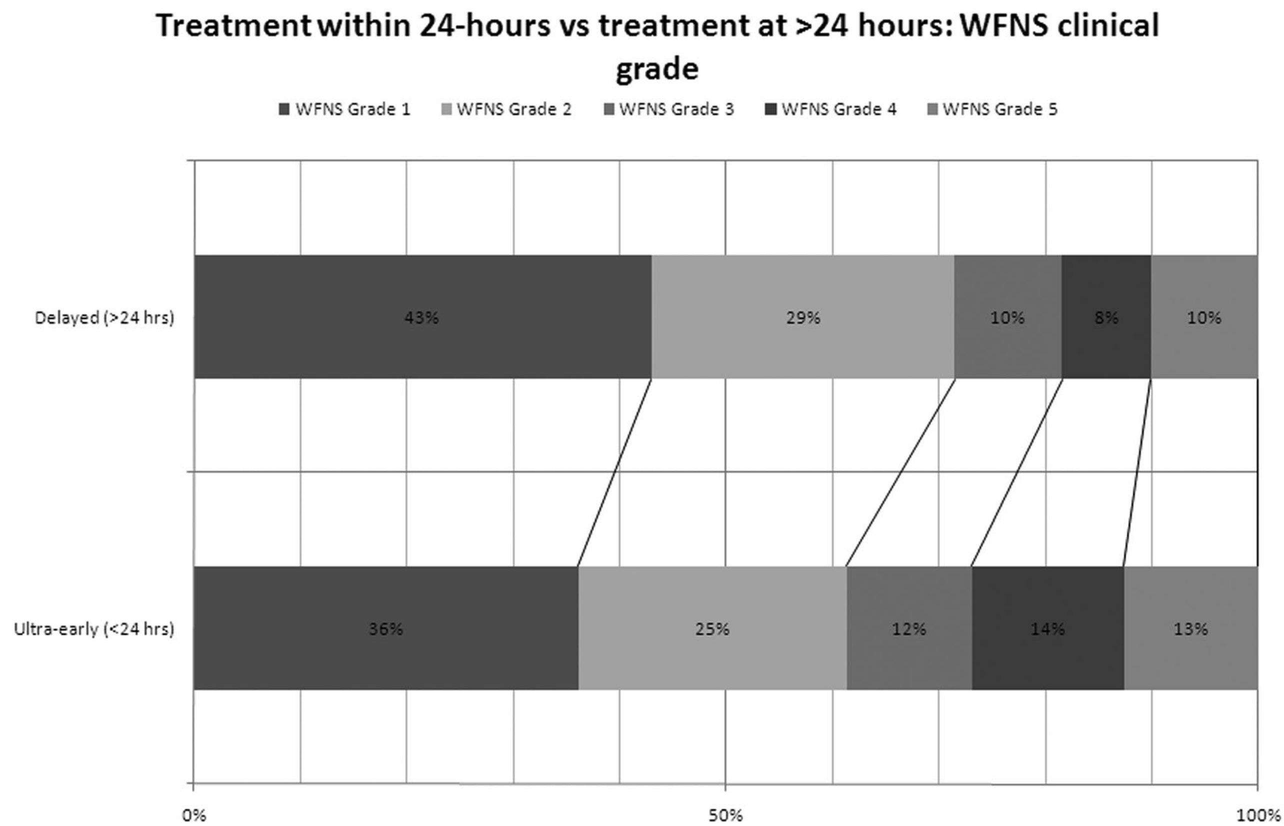

Figure 1. Bar graph illustrating the spread of WFNS clinical grades within the groups defined by treatment within 24 hours (ultra-early) and beyond 24 hours (not ultra-early). The higher proportion of higher WFNS grades in the ultra-early group is statistically significant (Mantel-Haenszel test for linear association, $P=0.029$). WFNS indicates World Federation of Neurological Societies.

ruptured aneurysms treated with endovascular coiling increased from a mean of 20% from 1997 to 2002 to 59% through 2003 to 2007 (χ^2, $P=0.000$).

All coiling cases were performed by subspecialist neurointerventionists under general anesthetic and systemic heparinization. The neurointervention unit provides a 24-hour a day service with on-call neurointerventionists and appropriately trained nursing staff and radiographers. Surgical cases were operated on by standard microneurosurgical clipping techniques.

Prophylactic nimodipine is a protocol-driven part of the medical management of standard SAH in this institution. Symptomatic hydrocephalus was managed with ventriculostomy, ventriculoperitoneal shunt, or lumbar puncture if judged appropriate on a case-by-case basis. The treatment of vasospasm and delayed ischemic neurological deficits was managed on a case-by-case basis and included induced hypertension, hypervolemia, hemodilution, intracranial intra-arterial calcium channel blockers, and endoluminal angioplasty.

Results

Ruptured Aneurysms Treated Within 24 Hours (Ultra-early)

Two hundred thirty cases were treated with coiling or clipping within 24 hours of the aneurysmal SAH ictus, referred to as ultra-early. In the other 229 cases, coiling or clipping was performed >24 hours after SAH, referred to in this article as delayed.

As detailed in the previous section, the cases in the delayed group do not represent a clinical decision to delay treatment, but rather cases that were delayed by varying nonclinical factors. Of these delayed cases, 88% were treated within 3 days (previously defined as "early" in the literature[2,7,12–28]), 8% between days 4 and 10 (previously defined as "intermediate" in the literature[2,7,12–28]), and 4% at >10 days (previously defined as "late" in the literature[2,7,12–28]). We use the unifying term "delayed" to group all the cases that were treated at >24 hours after SAH.

Table 1 details the data breakdown between the 2 groups and the probability values generated by statistical tests of their differences.

Similar Demographics and Aneurysm Characteristics in the Ultra-Early and Delayed Groups

Statistical analysis demonstrated no significant difference in age, gender, smoking, family history of SAH, aneurysm size, or aneurysm location between those treated within 24 hours (ultra-early) and those treated >24 hours (delayed). Of those cases treated by coiling, there was no significant difference in the use of balloon assistance or stent assistance between the 2 groups.

WFNS Grades Significantly Higher in the Ultra-Early Group

WFNS clinical Grades 3, 4, and 5 were more often treated ultra-early (54%, 63%, and 56%, respectively), whereas WFNS Grades 1 and 2 were not (46% and 47%). This trend is significant when tested with the Mantel-Haenszel test for linear association ($P=0.029$). In clinical parlance, WFNS

Table 2. Patient Demographics, Case Characteristics, Treatment Modality, and Treatment Timing: Comparison of Cases Grouped by Clinical Outcome at 6 Months, Independence (mRS 0–2), Dependence, or Death (mRS 3–6)*

	All Cases		Clinical Outcome at 6 Mo				Statistical Test	
			mRS 0–2		mRS 3–6		(mRS 0–2 vs mRS 3–6)	
	Mean (SD)	n (row %)	Mean (SD)	n (row %)	Mean (SD)	n (row %)	*P*	Test Used
Total no. of cases		408		362 (89%)		46 (11%)		
Age on admission, y	53 (14.4)		51 (13.4)		67 (11.4)		0.000	Independent *t* test
Gender								
Female		263 (64%)		230 (87%)		33 (13%)	0.274	Pearson χ^2
Male		145 (36%)		132 (91%)		13 (9%)		
		408		362 (89%)		46 (11%)		
Smoking status								
Smoker		90 (22%)		84 (93%)		6 (7%)	0.128	Pearson χ^2
Nonsmoker		315 (78%)		276 (88%)		39 (12%)		
		405		360 (89%)		45 (11%)		
FHx SAH								
FHx of SAH		10 (2%)		9 (90%)		1 (10%)	0.910	Pearson χ^2
No FHx of SAH		395 (98%)		351 (89%)		44 (11%)		
		405		360 (89%)		45 (11%)		
WFNS clinical grade								
1		166 (41%)		161 (97%)		5 (3%)	0.000	Mantel-Haenszel
2		108 (27%)		102 (94%)		6 (6%)		Pearson χ^2
3		41 (10%)		34 (83%)		7 (17%)		
4		43 (11%)		31 (72%)		12 (28%)		
5		49 (12%)		33 (67%)		16 (33%)		
		407		361 (89%)		46 (11%)		
WFNS dichotomized								
Good clinical grade (WFNS 1–3)		315 (77%)		297 (94%)		18 (6%)	0.000	Pearson χ^2
Poor clinical grade (WFNS 4–5)		92 (23%)		64 (70%)		28 (30%)		
		407						
Fisher grade								
1		22 (10%)		22 (100%)		0 (%)	0.009	Mantel-Haenszel
2		33 (15%)		32 (97%)		1 (3%)		Pearson χ^2
3		63 (29%)		58 (92%)		5 (8%)		
4		100 (46%)		81 (81%)		19 (19%)		
		218		193 (89%)		25 (11%)		
Fisher grade dichotomized								
Fisher 1 and 2		55 (25%)		54 (98%)		1 (2%)	0.009	Pearson χ^2
Fisher 3 and 4		163 (75%)		139 (85%)		24 (15%)		
Aneurysm size, mm	6.8 (3.8)		6.7 (3.6)		8.5 (5.8)		0.136	Independent *t* test
Aneurysm location								
Posterior circulation		57 (17%)		51 (89%)		6 (11%)	0.369	Pearson χ^2
ICA, ACA, AComA		148 (45%)		133 (90%)		15 (10%)		
MCA		125 (38%)		106 (85%)		19 (15%)		
		330		72 (22%)		6 (2%)		
Aneurysm location dichotomized								
Anterior circulation		351 (86%)		311 (89%)		40 (11%)	0.847	Pearson χ^2
Posterior circulation		57 (14%)		51 (89%)		6 (11%)		
		408		362 (89%)		46 (11%)		

(*Continued*)

Table 2. Continued

	All Cases		Clinical Outcome at 6 Mo				Statistical Test (mRS 0–2 vs mRS 3–6)	
			mRS 0–2		mRS 3–6			
	Mean (SD)	n (row %)	Mean (SD)	n (row %)	Mean (SD)	n (row %)	*P*	Test Used
Timing category (dichotomized)								
Ultra-early (<24 h)		199 (49%)		183 (92%)		16 (8%)	0.044	Pearson χ^2
Delayed (>24 h)		209 (51%)		179 (86%)		30 (14%)		
		408		362 (89%)		46 (11%)		
Timing categories								
Ultra-early (<24 h)		199 (49%)		183 (92%)		16 (8%)	0.032	Pearson χ^2
Early (1–3 d)		183 (45%)		160 (87%)		23 (13%)		
Intermediate (4–10 d)		18 (4%)		13 (72%)		5 (28%)		
Late (>10 d)		8 (2%)		6 (75%)		2 (25%)		
		408		362 (89%)		46 (11%)		
Treatment method								
Clipped		260 (64%)		227 (87%)		33 (13%)	0.230	Pearson χ^2
Coiled		148 (36%)		135 (91%)		13 (9%)		
		408		362 (89%)		46 (11%)		

mRS indicates modified Rankin Scale; FHx, family history; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurological Societies; ICA, internal carotid artery; ACA, anterior cerebral artery; AComA, anterior communicating artery; MCA, middle cerebral artery.

*The results are then grouped into independence (mRS 0–2) and dependence or death (mRS 3–6) at 6 mo. The right-hand columns are the results of the relevant statistical tests applied to the difference between the groups.

grades are often dichotomized into "good grade" (WFNS 1 to 3) and "poor grade" (WFNS 4 to 5). More of the ultra-early group was WFNS 4 to 5 (27%) than the not ultra-early group (18%; χ^2, P=0.029). This is graphically illustrated in Figure 1.

Fisher CT Grade Significantly Higher in the Ultra-Early Group

Fisher CT grade was only recorded for 243 cases. Eighty-three percent of cases treated within 24 hours (ultra-early) were Fisher Grade 3 or 4 compared with 65% of those treated at >24 hours (delayed; Table 1). This difference was statistically significant (χ2, P=0.001).

Coiling Was More Often Performed Within 24 Hours Than Clipping

One hundred sixty-eight aneurysms were coiled and 291 were clipped over the study period. Sixty-one percent (102 of 168) of the coiled aneurysms were treated within 24 hours of SAH (ultra-early) compared with 44% (102 of 168) of the clipped aneurysms (χ^2, P=0.001).

Predictors of Clinical Outcome at 6 Months (mRS)

Table 2 details the demographic and clinical variables of the 2 outcome groups and the results of statistical tests of their differences.

Outcome Did Not Differ Significantly Over the 11 Years

A total of 8.8% (16 of 182) of patients treated after 2002 were dead or dependent at 6 months compared with 13.3% (30 of 226) of patients treated before 2002; however, this was not statistically significant (χ^2, P=0.155).

Increasing Age Is Associated With a Poor Outcome

The mean age of patients who were dead or dependent at 6 months post-SAH is 67 years (SD 11.4) compared with 51 years (SD 13.4) in the group that is independent (P=0.000, *t* test).

WFNS Clinical Grade Predicts Clinical Outcome at 6 Months

As expected, the WFNS clinical grade was a predictor of clinical outcome (mRS) at 6 months. This is tabulated in Table 2. Patients with poor clinical grade (WFNS 4 to 5) were dead or dependent at 6 months (mRS 3 to 6) in 30.4% of cases compared with 5.7% of good clinical grade (WFNS 1 to 3) cases (Mantel-Haenszel test for linear association, P=0.029).

Fisher CT Grade Predictive to Clinical Outcome at 6 Months

Increasing Fisher CT grade was significantly associated with a higher incidence of death or dependence at 6 months. Fifteen percent of patients with Fisher CT Grade 3 or 4 on their admission CT scan were dead or dependent (mRS 3 to 6) at 6 months compared with 1.8% of patients with Fisher CT Grades 1 or 2 (χ^2, P=0.009). Fisher CT grade and outcome data were only available for 218 patients.

Treatment Within 24 Hours Was Associated With Improved Clinical Outcome at 6 Months

Treatment within 24 hours was associated with a shift toward better (lower) mRS scores at 6 months. This is graphically illustrated in Figure 2 and is statistically significant (Mantel-Haenszel test for linear association, P=0.024).

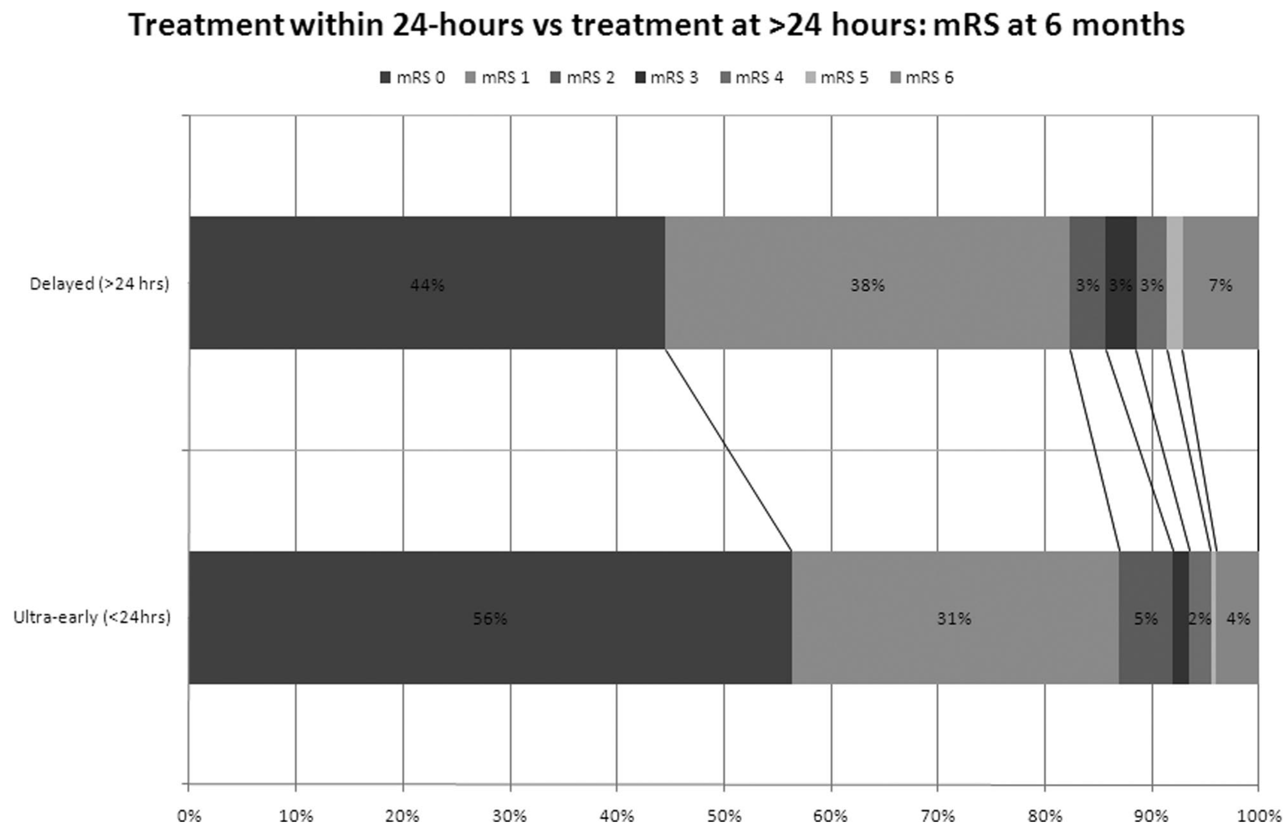

Figure 2. Clinical outcome at 6 months measured by the modified Rankin Scale (mRS) for the ultra-early (coiling or clipping within 24 hours of SAH) and not ultra-early (coiling or clipping at >24 hours post-SAH) groups. The "outcome shift" toward better outcomes in the ultra-early group is statistically significant (P=0.024) when tested with the Mantel-Haenszel test for linear association. SAH indicates subarachnoid hemorrhage.

Dichotomizing the mRS outcome data into independent (mRS 0 to 2) and dead or dependent (mRS 3 to 6) also demonstrated a significant difference.

Eight point zero percent (16 of 199) of cases treated within 24 hours of SAH (ultra-early) were dependent or dead at 6 months compared with 14.4% (30 of 209) of those treated at >24 hours post-SAH (delayed; χ^2, P=0.044).

The relative risk reduction in dependency or death associated with ultra-early versus delayed treatment was 44.0%. The absolute reduction in risk of death or dependence was 6.4% (relative risk, 0.560; 95% CI, 0.315 to 0.995; P=0.044).

Subgrouping the delayed cases based on the treatment timing categories previously defined in the literature[2,7,12–28] also generated significant results. Eight point zero percent (16 of 199) of cases treated within 24 hours, 12.6% (23 of 183) of cases treated at 1 to 3 days, 27.8% (5 of 18) of cases treated at 4 to 10 days, and 25.0% (2 of 8) of cases treated at >10 days were dependent or dead at 6 months (χ^2, P=0.032). The 36.5% relative risk reduction and 4.6% absolute risk reduction associated with ultra-early treatment (within 24 hours) versus "early" treatment (at 1 to 3 days) did not achieve statistical significance (χ^2, P=0.144).

Multivariate Analysis

Stepwise introduction of the significant variables into a logistic regression multivariate model resulted in statistical significance for age (P=0.000; OR, 1.107; 95% CI, 1.070 to 1.146), WFNS clinical grade (P=0.000; OR, 2.209; 95% CI, 1.698 to 2.890), and ultra-early treatment (P=0.041; OR, 2.241; 95% CI, 1.032 to 4.867).

Subgroup Analysis: Coiling

Subgroup analysis of patients treated within 24 hours by coiling (ultra-early coiling) demonstrated a more exaggerated outcome shift toward better mRS scores relative to patients coiled at >24 hours (delayed coiling; Mantel-Haenszel, P=0.001). This is graphically illustrated in Figure 3.

Dichotomizing the mRS outcome data into independent (mRS 0 to 2) and dead or dependent (mRS 3 to 6) also demonstrated a significant difference.

A total of 3.5% (3 of 86) of cases coiled within 24 hours of SAH (ultra-early coiling) were dependent or dead at 6 months compared with 16.1% (10 of 62) of those coiled at >24 hours post-SAH (delayed coiling; χ^2, P=0.007).

The relative risk reduction in dependency or death associated with ultra-early coiling versus delayed coiling was 78.3%. The absolute reduction in risk of death or dependence was 12.6%. (relative risk, 0.216; 95% CI, 0.062 to 0.754; P=0.007).

Subgrouping the coiling cases into the timing categories previously discussed generated significant results. A total of 3.5% (3 of 86) of cases coiled within 24 hours, 12.5% (7 of 56) of cases coiled at 1 to 3 days, 50.0% (2 of 4) of cases coiled at 4 to 10 days, and 50.0% (1 of 2) of cases coiled at >10 days were dependent or dead at 6 months (χ^2, P=0.001).

Ultra-early coiling (within 24 hours) is associated with an 82% relative risk reduction and 10.2% absolute risk reduction when

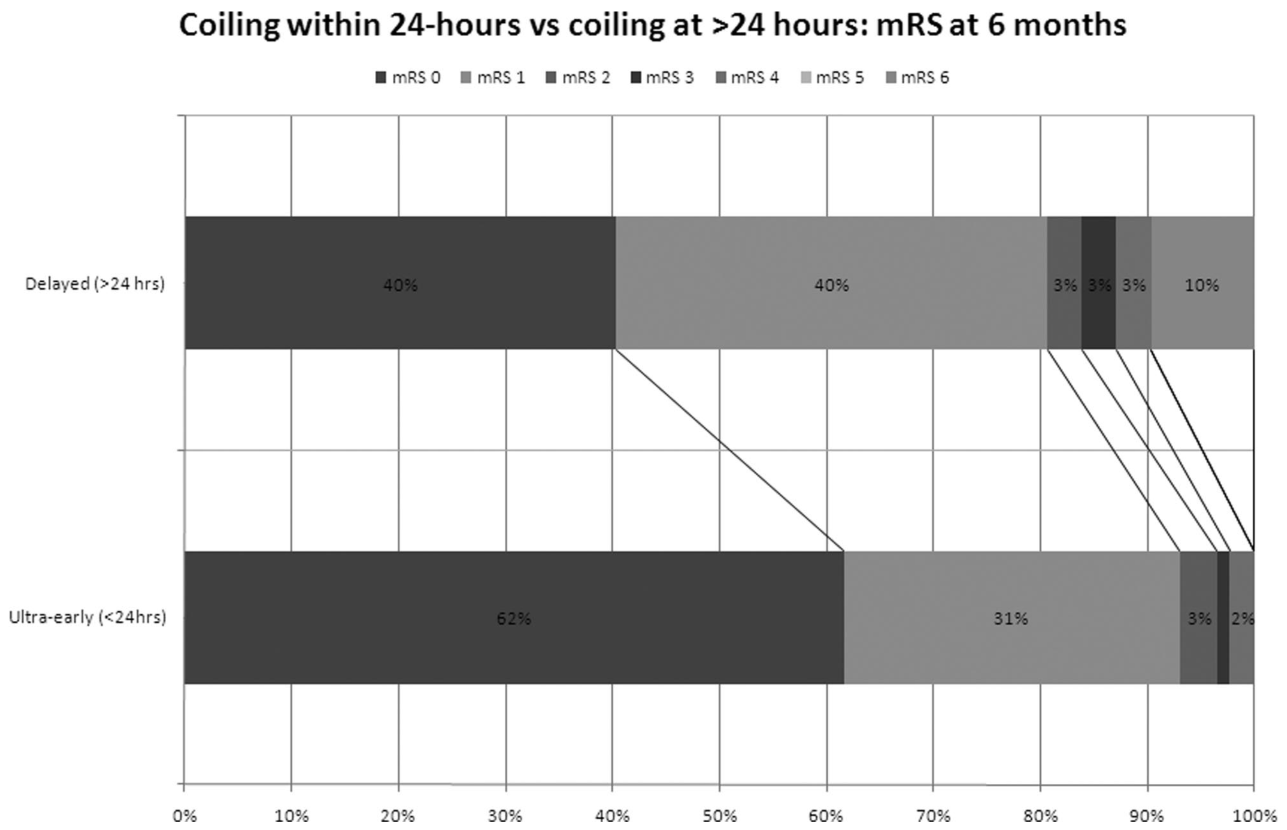

Figure 3. Subgroup analysis: endovascular coiling cases. Clinical outcome at 6 months measured by the modified Rankin Scale (mRS) for the ultra-early (coiling within 24 hours of SAH) and not ultra-early (coiling at >24 hours post-SAH) groups. The "outcome shift" toward better outcomes in the ultra-early group is statistically significant (P=0.001) when tested with the Mantel-Haenszel test for linear association. SAH indicates subarachnoid hemorrhage.

compared with "early" coiling (at 1 to 3 days). This is statistically significant (χ^2, P=0.040). This is graphically illustrated in Figure 4.

Noteworthy is that these 2 groups (ultra-early coiling and early coiling) do not differ significantly in patient age (t test, P=0.501), WFNS clinical grade (χ^2, P=0.813), smoking status (χ^2, P=0.593), family history of SAH (χ^2, P=0.605), aneurysm location (χ^2, P=0.312), or aneurysm size (t test, P=0.420). A higher proportion of the cases coiled within 24 hours (88.0% [44 of 50]) were of poor Fisher CT grade (3 or 4) than the cases coiled at 1 to 3 days (62.1% [18 of 29]). This was significant (χ^2, P=0.007).

Subgroup Analysis: Clipping

A total of 11.5% (13 of 113) of cases clipped within 24 hours after SAH (ultra-early clipping) were dead or dependent at 6 months compared with 13.6% (20 of 147) of cases clipped >24 hours (delayed clipping); however, this was not statistically significant. Overall, 87% of clipped cases were independent at 6 months compared with 91% of coiled cases, but this was not statistically significant.

Discussion

The timing of treatment of ruptured aneurysms has been debated for decades. Definitions have evolved for particular time intervals that have variably been considered better or worse options throughout the last half century. Late surgery usually refers to >10 days post-ictus; intermediate surgery refers to days 4 to 10; early surgery refers to the first 3 days; and ultra-early surgery refers to surgery within the first 24 hours.[2,3,7,8,10, 12–20,22,23,25,35] We refer to all treatment after the first 24 hours as delayed, a group that encompassed the previously defined early, intermediate, and late timings. Eighty-eight percent of the delayed group were treated between 1 and 3 days post-ictus.

After the initial SAH, repeat SAH (synonymous with rebleed or rebleeding) is the biggest cause of morbidity and poor outcome. In patients who survive the initial hemorrhage, rebleeding is also the major cause of death.[11,36–40]

For almost 20 years there has been evidence that most rebleeds and indeed the most dangerous rebleeds occur in the first 24 hours after SAH (ultra-early rebleeding). Multiple retrospective and prospective studies have shown the incidence of rebleeding is maximal in the first 24 hours with rates of 4.1% to 17.3% reported. Most studies recording outcomes associated with ultra-early rebleeding have demonstrated incidences of >10% and case-fatality rates approaching 65%, some as high as 80%.[3–10,21,41]

The evidence for securing ruptured aneurysms with neurosurgical clipping or endovascular coiling to prevent rebleeding is sound, and there is evidence from the International Subarachnoid Hemorrhage Trial that endovascular coiling is the preferred method when both techniques are equally suited.[21,31–34,42–47]

Logically, therefore, it follows that securing the aneurysm with endovascular coiling or neurosurgical clipping in the

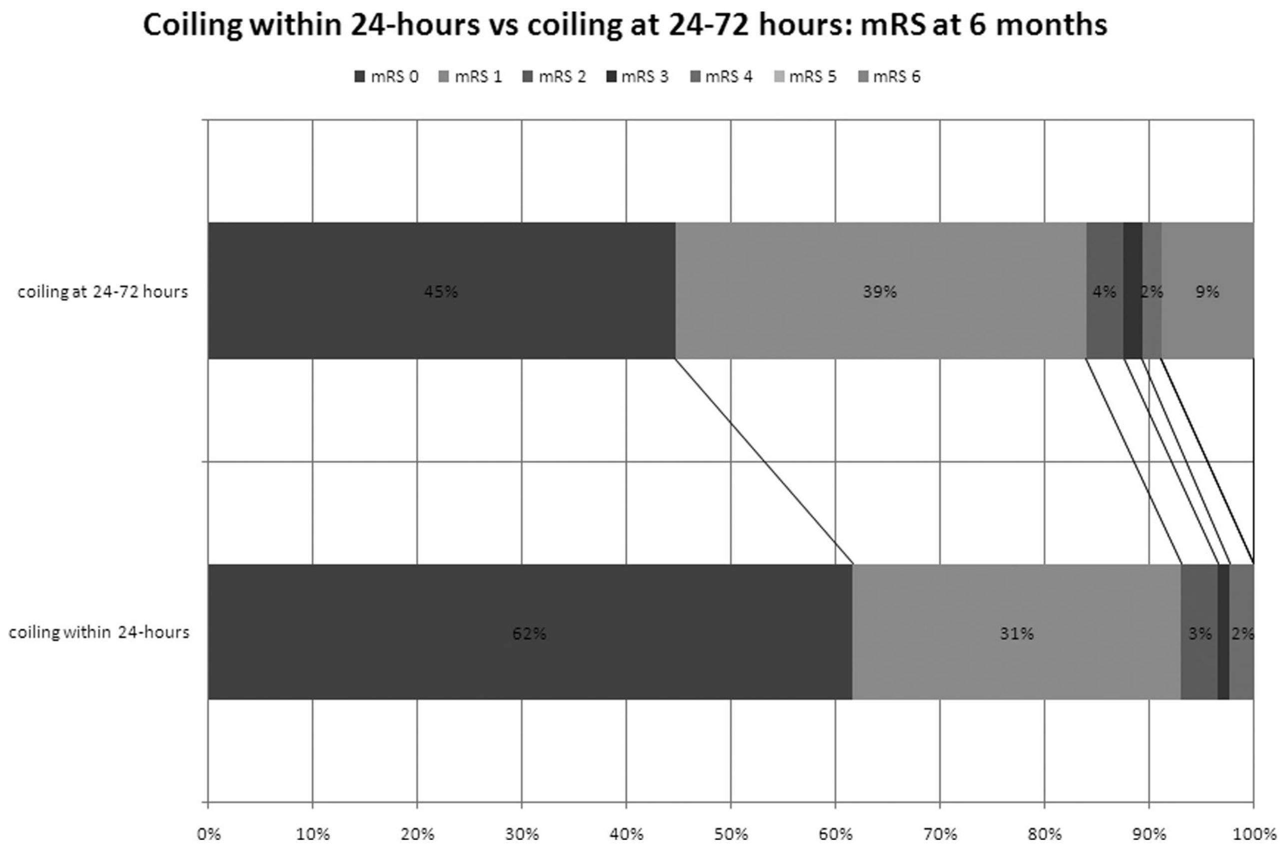

Figure 4. Subgroup analysis: endovascular coiling cases. Clinical outcome at 6 months measured by the modified Rankin Scale (mRS) for the ultra-early coiling (within 24 hours of SAH) and early coiling (at 1 to 3 days post-SAH) groups. The "outcome shift" toward better outcomes in the ultra-early group is statistically significant ($P=0.006$) when tested with the Mantel-Haenszel test for linear association. SAH indicates subarachnoid hemorrhage.

first 24 hours after SAH will reduce the risk of rebleeding. Earlier coiling or clipping of the aneurysm also means that aggressive medical or endovascular therapy for vasospasm/delayed ischemic neurological deficits can be started promptly.[38–40]

This outcome benefit associated ultra-early treatment compared with delayed treatment in this series is despite the higher proportion of patients with poor WFNS clinical grade in the ultra-early treatment group.

The reason that more patients with poor WFNS clinical grade were treated within 24 hours is at least partly related to the delays often experienced in arranging anesthetics for patients with good clinical WFNS grade (conscious patients). The patient with poor WFNS clinical grade, already intubated and ventilated in the emergency room, is often transferred to the neuroangiography suite or operating room more promptly. We have anecdotally observed a similar phenomenon in transfers from other hospitals. Patients with poor WFNS clinical grade SAH are often triaged as higher priority for helicopter or fixed-wing transfer.

In this series, the outcome benefit associated with ultra-early treatment was more pronounced for coiling. In the neurosurgical literature debating surgical timing over the past half century, the perceived higher risks of early (in the first 3 days) relative to late (>10 days) aneurysm surgery were anecdotally attributed to the unfavorable operating conditions after recent SAH. The acutely swollen, soft, hyperemic, poorly autoregulating brain was considered more prone to laceration, contusion, and infarction secondary to retraction.[1,2,19,22,23,25] Endovascular coiling avoids the need for surgical retraction, and this may be a factor in the higher outcome benefit observed for ultra-early coiling. Other studies have also concluded that early coiling is safe.[13,18]

Anecdotally the experience of the neurosurgeons in our institution is that craniotomy within 24 hours is not usually associated with unmanageable brain swelling.

The primary limitations of this study are those normally associated with retrospective analyses. However, we believe there is minimal if any selection bias is present in the grouping of these cases. The policy of the neurosurgeons and neurointerventionists at this institution is that ruptured aneurysms are treated within 24 hours whenever possible. The nonclinical interhospital and intrahospital delays described apply a degree of randomization to the groups. This is reflected in the statistically matched demographics and aneurysm characteristics between the 2 groups.

In summary, this study provides evidence that treatment of ruptured intracranial aneurysms within 24 hours of aneurysmal SAH improves medium- and long-term clinical outcome. The benefit of ultra-early treatment is even more apparent for patients treated with endovascular coiling.

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