The International Cooperative Study on the Timing of Aneurysm Surgery

The North American Experience

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Background and Purpose: **The timing of aneurysm surgery after subarachnoid hemorrhage is a major neurosurgical controversy addressed by the International Cooperative Study on the Timing of Aneurysm Surgery (1980–1983). The present report examines the results of this trial in the subgroup of patients admitted to North American centers.**

Methods: **The method of study was a large, multicenter, prospective, epidemiological survey. Neurosurgeons were required to indicate prospectively the interval to planned aneurysm surgery at the time of patient admission. Outcome at 6 months was determined by a blinded evaluator, and overall management results were analyzed by the planned surgical interval.**

Results: **Seven hundred seventy-two (21.9% of the total study population) patients admitted from days 0 to 3 after subarachnoid hemorrhage were accrued in North American centers. Overall outcome in patients planned for surgery in days 0–3 was equivalent in terms of mortality (after adjustment for prognostic variables) to patients planned for days 11–32, but the early patients had significantly improved rates of good recovery (70.9% versus 61.7%, $p<0.01$). Patients planned for surgery during the days 7–10 interval had nearly twice the mortality of patients in the other intervals.**

Conclusions: **In contrast to the results from the overall trial, which found no difference between early and delayed surgery, results were best in North American centers when surgery was planned between days 0 and 3 after subarachnoid hemorrhage. These findings argue strongly for early diagnosis and referral for surgical intervention of North American patients suspected of having a ruptured cerebral aneurysm. (*Stroke* 1992;23:205–214)**

In the early 1980s, the optimal timing of surgery for ruptured cerebral aneurysms was the subject of considerable controversy.[1] The majority opinion in North America at that time was that the best results were obtained when the operation could be delayed until the clinical condition of the patient was stable and the reactive brain swelling accompanying the initial hemorrhage had subsided.[2,3] On the other hand, others argued that delaying surgery resulted in too much attrition from rebleeding from the aneurysm and that early surgery for clipping of the aneurysm could be performed with acceptable results.[4,5] In an effort to address this issue, a large, nonrandomized, prospective epidemiological survey, the International Cooperative Study on the Timing of Aneurysm Surgery, was organized.[6,7]

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Subjects and Methods

From 1980 through 1983, 3,521 patients were entered into the survey in 68 neurosurgical centers in 14 countries. Participating neurosurgeons were required to prospectively choose a planned interval to aneurysm surgery at the time of patient admission to the hospital. Morbidity and mortality were then assessed by a blinded evaluator at 6 months after the hemorrhage, and the results were analyzed by planned and actual surgery intervals. The overall results of this study have been published previously.[6,7] The experience in the 27 neurosurgical centers in the United States and Canada (see Appendix A) is the subject of this report.

Details of the methodology used for the conduct of this study may be found in the previous reports.[6,7] The study was designed to examine differences in overall management results as they pertained to surgical timing and to evaluate outcomes on all patients regardless of whether they underwent surgery or not.[1] Thus, a study

design analogous to the "intent to treat" paradigm was used, whereby neurosurgeons were required to specify the planned time for aneurysm surgery prospectively at the time of patient admission. This approach avoids the selection bias inherent in analysis of only those patients undergoing operation, who customarily are chosen because of their relatively good preoperative conditions, and accounts for those patients who never undergo operation because they die or are neurologically ruined by rebleeding or vasospasm prior to their planned surgery. The results in those patients actually undergoing surgery are also reported here only to provide a comparison with other purely surgical series.

Briefly, eligible patients were admitted to a participating center on days 0–3 after their first major subarachnoid hemorrhage (SAH) from a saccular aneurysm (day 0 is the calendar day of the hemorrhage). Exclusion criteria included SAH from a fusiform, mycotic, or traumatic aneurysm or from unknown cause, need for emergency evacuation of an intracranial hematoma, and severe complicating medical illnesses on admission.

After completion of the initial examination, surgeons were required to specify at which time interval they planned to conduct surgery for treatment of the aneurysm. Intervals that could be chosen were days 0–3, days 4–6, days 7–10, days 11–14, days 15–32, and no surgery planned. The actual surgery, when and if performed, was conducted as required by the patient's clinical condition and neurological status. However, for the overall management results, all subsequent medical, neurological, and surgical complications were attributed to the planned surgery interval.

Outcome at 6 months after the initial hemorrhage was assessed using the Glasgow Outcome Scale[8] by an evaluator who was blinded to the patient's hospital course and planned surgery interval. The participating surgeon also designated the primary cause of death or disability. Audit of a 24% sample of the Glasgow Outcome Scale scores confirmed excellent agreement with the evaluator assessments.

Standardized forms were used to collect data on demographic information, initial neurological condition, results of angiography and head computed tomography (CT) scanning, preoperative and postoperative medications and other interventions (e.g., cerebrospinal fluid drainage), neurological complications including rebleeding and vasospasm, and complications of medical and surgical therapy. Focal ischemic deficits from all causes were tabulated.

Comparison of groups with categorical variables was done with contingency table methods and significance determined by a χ^2 test.[9] Continuous variables were compared using a t test, and significance was determined by the t distribution. Adjusted results of mortality and good recovery were calculated using proportional hazards regression with prognostic variables and center variables as covariates. The prognostic variables used were derived from an analysis of the outcomes from the first half of the overall study[6] and included admission neurological condition, age, preexisting medical conditions, systolic blood pressure on admission, thickness of SAH clot on admission CT scan, presence of intracerebral or intraventricular clot on admission CT scan, aneurysm site, and presence of angiographic vasospasm on admission angiogram. Center effects were determined from regression of prognostic and treatment variables and comparison of observed and expected results. Significance of adjusted results was determined using the log likelihood statistic with comparison to a χ^2 distribution.[10]

TABLE 1. Admission Neurological Status of Patients From North American Versus Other Centers

	North American centers		Other centers	
	n	%	*n*	%
Level of consciousness				
Alert	355	46.0	1,367	49.7
Drowsy	260	33.7	876	31.9
Stuporous	87	11.3	261	9.5
Comatose	70	9.1	245	8.9
Speech				
Normal	584	75.6	2,059	74.9
Dysphasic	49	6.4	245	8.9
No verbal response	139	18.0	445	16.2
Orientation				
Normal	467	60.5	1,613	58.7
Impaired	305	39.5	1,136	41.3
Response to commands				
Appropriate	572	74.1	2,048	74.5
Inappropriate	200	25.9	701	25.5
Motor response				
Normal	572	74.1	2,097	76.3
Mild focal deficit	101	13.1	320	11.6
Severe focal deficit	35	4.5	163	5.9
Abnormal flexor	20	2.6	48	1.8
Abnormal extensor	34	4.4	77	2.8
No response	10	1.3	44	1.6

Results

Of the 3,521 patients admitted to the entire study, 772 (21.9%) were admitted from the North American centers. The patients in North America were compared with those elsewhere. The mean±SD age of the patients in North America was 49.2±14.3 years. The degree of female preponderance was greater in North American centers (68.3%) than in other geographical regions (59.1%, $p<0.001$). A greater percentage of patients in North America were admitted on the same calendar day as the hemorrhage (57.6% versus 46.4%, $p<0.001$).

Preexisting medical conditions were reported with approximately the same frequency in North America as in other geographic regions. Hypertension was the most commonly reported preexisting illness (24%).

Only 46% of the patients were fully alert on admission, but nearly three fourths had no motor or

TABLE 2. Preoperative and Postoperative Medications Administered to Patients From North American Other Centers

	North American centers		Other centers		
	n	%	*n*	%	*p*
Preoperative medications					
Antihypertensives	329	42.6	649	23.6	<0.001
Sedatives	411	53.2	802	29.2	<0.001
Anticonvulsants	447	57.9	911	33.1	<0.001
Narcotic analgesics	312	40.4	362	13.2	<0.001
Antifibrinolytics	412	53.4	1,031	37.5	<0.001
Steroids	545	70.6	1,068	38.9	<0.001
Mannitol	110	14.3	592	21.5	<0.001
Diuretics	104	13.5	172	6.3	<0.001
Vasopressor agents	36	4.7	55	2.0	<0.001
Hypervolemia	150	19.4	125	4.6	<0.001
Isuprel	20	2.6	14	0.5	<0.001
Aminophylline	34	4.4	30	1.1	<0.001
Low molecular weight dextran	15	1.9	229	8.3	<0.001
Other	71	9.2	228	8.3	NS
Total patients with data	772		2,749		
Postoperative medications					
Antihypertensives	151	23.1	273	11.9	<0.001
Sedatives	91	13.9	216	9.5	<0.001
Anticonvulsants	393	60.1	1,283	56.2	NS
Narcotic analgesics	200	30.6	214	9.4	<0.001
Antifibrinolytics	14	2.1	172	7.5	<0.001
Steroids	486	74.3	1,466	64.2	<0.001
Mannitol	60	9.2	617	27.0	<0.001
Diuretics	49	7.5	145	6.4	NS
Vasopressor agents	69	10.6	178	7.8	0.025
Hypervolemia	253	38.7	342	15.0	<0.001
Isuprel	14	2.1	22	1.0	0.016
Aminophylline	20	3.1	43	1.9	NS
Low molecular weight dextran	67	10.2	725	31.7	<0.001
Other	74	11.3	479	21.0	<0.001
Total patients with data	654		2,284		
Postoperative or preoperative medications					
Antihypertensives	361	46.8	714	26.0	<0.01
Sedatives	428	55.4	867	31.5	<0.01
Anticonvulsants	529	68.5	1,537	55.9	<0.01
Analgesics	341	44.2	434	15.8	<0.01
Antifibrinolytics	414	53.6	1,118	40.7	<0.01
Steroids	659	85.4	1,808	65.8	<0.01
Mannitol	159	20.6	1,013	36.9	<0.01
Diuretics	144	18.7	267	9.7	<0.01
Vasopressor agents	100	13.0	222	8.1	<0.01
Hypervolemia	346	44.8	414	15.1	<0.01
Isuprel	33	4.3	34	1.2	<0.01
Aminophylline	50	6.5	62	2.3	<0.01
Dextran	79	10.2	804	29.3	<0.01
Other	103	13.3	600	21.8	<0.01

TABLE 3. Planned Versus Actual Surgery Intervals in North American and Other Centers

Actual surgery interval (days)	Planned surgery intervals (days)						
	0–3	4–6	7–10	11–14	15+	None	Total
North American centers							
0–3	237 90.8%	5 6.5%	3 1.8%	1 0.7%	0 0%	0 0%	246 31.9%
4–6	9 3.5%	51 66.2%	14 8.6%	1 0.7%	0 0%	1 1.6%	76 9.8%
7–10	2 0.8%	8 10.4%	62 38.0%	13 8.4%	0 0%	1 1.6%	86 11.1%
11–14	1 0.4%	3 3.9%	28 17.2%	48 31.2%	1 1.9%	4 6.3%	85 11.0%
15–32	3 1.1%	4 5.2%	27 16.6%	54 35.1%	30 56.6%	5 7.8%	123 15.9%
33+	2 0.8%	2 2.6%	5 3.1%	7 4.6%	11 20.8%	5 7.8%	32 4.1%
None	7 2.7%	4 5.2%	24 14.7%	30 19.5%	11 20.8%	48 75.0%	124 16.1%
Total	261 33.8%	77 10.0%	163 21.1%	154 19.9%	53 6.9%	64 8.3%	772 100.0%
Other centers							
0–3	1,226 91.9%	2 0.7%	2 0.4%	1 0.4%	1 0.5%	0 0%	1,232 44.8%
4–6	40 3.0%	218 73.9%	15 3.3%	2 0.7%	2 1.0%	0 0%	277 10.1%
7–10	11 0.8%	31 10.5%	214 46.6%	19 6.8%	5 2.6%	1 0.5%	281 10.2%
11–14	6 0.5%	12 4.1%	59 12.8%	99 35.5%	6 3.1%	2 1.1%	184 6.7%
15–32	17 1.3%	9 3.1%	53 11.6%	78 28.0%	75 38.7%	10 5.3%	242 8.8%
33+	4 0.3%	3 1.0%	17 3.7%	7 2.5%	23 11.9%	4 2.1%	58 2.1%
None	30 2.3%	20 6.8%	99 21.6%	73 26.2%	82 42.3%	171 91.0%	475 17.3%
Total	1,334 48.5%	295 10.7%	459 16.7%	279 10.1%	194 7.1%	188 6.8%	2,749 100.0%

speech deficit (Table 1). The admission neurological status of the patients in North America was remarkably similar to that of patients in the other geographical regions. Subarachnoid clot was present on admission CT scan in 83.1% of North American patients, a frequency similar to that reported from the other regions (85.8%). Intraventricular clot (20.9% versus 15.6%) and hydrocephalus (19.1%

TABLE 4. Preoperative and Postoperative Neurological Complications in North American and Other Centers

	North American centers		Other centers		
Complication	*n*	*%*	*n*	*%*	*p*
Rebleeding	83	10.8	295	10.7	NS
Focal ischemic deficit	269	34.8	724	26.3	<0.01
Angiographic complications	14	1.8	58	2.1	NS
Brain swelling	105	13.6	272	9.9	<0.01
Epidural hematoma	8	1.0	17	0.6	NS
Hydrocephalus	143	18.5	323	11.8	<0.01
Iatrogenic arterial occlusion	16	2.1	38	1.4	NS
Intracerebral hemorrhage	85	11.0	198	7.2	<0.01
Brain contusion	14	1.8	28	1.0	NS
Seizures	53	6.9	105	3.8	<0.01
Subdural hematoma	24	3.1	38	1.4	<0.01

versus 14.2%) were seen more frequently on admission CT scans in North America ($p<0.001$).

The size, distribution, and number of aneurysms demonstrated on the initial angiograms of the North American patients were similar to those reported in other large series.[11] Seventy-nine percent had a single aneurysm, and most (73.7%) were <12 mm in diameter. One third (33.9%) were located on the internal carotid artery, whereas 35.3% arose from the anterior cerebral/anterior communicating artery complex. Although the absolute frequencies were relatively low, North American patients were more likely to have giant aneurysms (3.2%) and basilar artery aneurysms (6.0%) than patients in other regions.

Table 2 lists the preoperative and postoperative medications administered. The most commonly used medications were steroids, anticonvulsants, sedatives, and antifibrinolytic agents. All of these drugs were administered more frequently in North America than in any other geographical region. The average number of medications administered preoperatively per patient in North America was 2.8. Hypervolemia (volume expansion) was used either preoperatively or postoperatively in 44.8% of pa-

TABLE 5. Preoperative and Postoperative Medical Complications in North American and Other Centers

	North American centers		Other centers		
Complication	*n*	*%*	*n*	*%*	*p*
Adult respiratory syndrome	27	3.5	43	1.6	<0.01
Anemia	24	3.1	150	5.5	<0.01
Angina	3	0.4	17	0.6	NS
Arrhythmia	56	7.3	72	2.6	<0.01
Asthma	9	1.2	33	1.2	NS
Atelectasis	47	6.1	34	1.2	<0.01
Bleeding disorder	8	1.0	28	1.0	NS
Cardiac failure	15	2.0	55	2.0	NS
Diabetes mellitus	23	3.0	53	2.0	NS
Gastrointestinal bleeding	20	2.6	111	4.0	NS
Hepatic failure	2	0.3	66	2.4	<0.01
Hepatitis	0	0.0	38	1.4	<0.01
Hypertension	204	26.4	441	16.0	<0.01
Hypotension	45	5.8	60	2.2	<0.01
Inappropriate antidiuretic hormone	63	8.2	64	2.3	<0.01
Myocardial infarction	7	0.9	18	0.7	NS
Pneumonia	64	8.3	183	6.7	NS
Pulmonary edema	32	4.2	29	1.1	<0.01
Renal failure	9	1.2	15	0.6	<0.01
Thrombophlebitis	20	2.6	41	1.5	NS
Cerebral hemorrhage	32	4.2	34	1.2	<0.01
Cerebral ischemia	319	41.3	779	28.3	<0.01

TABLE 6. Overall Management Outcome in North American and Other Centers

Outcome	North American centers		Other centers		*p*
	n	%	*n*	%	
Unadjusted mortality rates					
14 days	90	11.7	426	15.5	0.009
90 days	161	20.9	695	25.3	0.013
6 months	168	21.8	738	26.9	0.005
Adjusted 6 months*	...	20.6	...	27.3	0.0003
Unadjusted Glasgow Outcome Scale scores†					
Good recovery	451	58.4	1,576	57.3	0.034
Moderate disability	86	11.1	234	8.5	
Severe disability	47	6.1	147	5.4	
Vegetative	15	1.9	48	1.8	
Dead	173	22.4	744	27.1	

*Adjusted refers to mortality controlled for differences in prognostic variables between groups (see "Subjects and Methods").
†Follow-up in some cases >6 months.

TABLE 7. Primary Causes of Death and Disability by Planned Surgical Interval

	Planned surgery interval (days)												
	0–3		4–6		7–10		11–14		15–32		None		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*
Primary cause of death													
Direct effect	11	4.2	3	3.9	4	2.5	7	4.5	5	9.4	34	53.1	<0.001
Vasospasm	6	2.3	2	2.6	14	8.6	12	7.8	1	1.9	3	4.7	<0.05
Rebleeding	9	3.4	3	3.9	12	7.4	9	5.8	4	7.5	5	7.8	NS
Hydrocephalus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	NS
Intracerebral hematoma	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0	NS
Surgical complications	5	1.9	2	2.6	3	1.8	0	0.0	0	0.0	1	1.6	NS
Medical therapy complications	1	0.4	1	1.3	1	0.6	0	0.0	0	0.0	1	1.6	NS
Other	4	1.5	0	0.0	4	2.5	4	2.6	1	1.9	0	0.0	NS
Primary cause of disability													
Direct effect	16	6.1	5	6.5	5	3.1	7	4.5	5	9.4	0	0.0	NS
Vasospasm	26	10.0	8	10.4	13	8.0	10	6.5	1	1.9	3	4.7	NS
Rebleeding	1	0.4	0	0.0	2	1.3	2	1.2	3	5.7	2	3.1	<0.001
Hydrocephalus	1	0.4	2	2.6	1	0.6	6	3.9	1	1.9	2	3.1	NS
Intracerebral hematoma	2	0.8	1	1.3	2	1.2	3	1.9	1	1.9	1	1.6	NS
Surgical complications	6	2.3	3	3.9	6	3.7	11	7.1	3	5.7	0	0.0	NS
Medical therapy complications	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	NS
Other	6	2.3	0	0.0	4	2.5	4	2.6	1	1.9	0	0.0	NS
Unknown	1	0.4	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	NS
Primary cause of death or disability													
Direct effect	27	10.3	8	10.4	9	5.5	14	9.1	10	18.9	34	53.1	<0.001
Vasospasm	32	12.3	10	13.0	27	16.6	22	14.3	2	3.8	6	9.4	NS
Rebleeding	10	3.8	3	3.9	14	8.6	11	7.1	7	13.2	7	10.9	0.05
Hydrocephalus	1	0.4	2	2.6	1	0.6	6	3.9	1	1.9	2	3.1	NS
Intracerebral hematoma	2	0.8	1	1.3	3	1.8	3	1.9	1	1.9	1	1.6	NS
Surgical complications	11	4.2	5	6.5	9	5.5	11	7.1	3	5.7	1	1.6	NS
Medical therapy complications	1	0.4	1	1.3	1	0.6	0	0.0	0	0.0	1	1.6	NS
Other	10	3.8	0	0.0	8	4.9	8	5.2	2	3.8	0	0.0	NS
Unknown	1	0.4	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	NS

For days 0–3 interval, $n=261$; days 4–6, $n=77$; days 7–10, $n=163$; days 11–14, $n=154$; days 15–32, $n=53$; None, $n=64$.

TABLE 8. Overall Outcome by Planned and Actual Surgery Interval

	Surgery interval (days)					
	0–3	4–6	7–10	11–14	15–32	*p*
Planned surgery interval						
Unadjusted						
Mortality	13.8%	14.3%	22.1%	20.1%	20.8%	<0.05
Good recovery	69.7%	63.6%	57.1%	55.2%	56.6%	<0.05
Adjusted						
Mortality	14.5%	15.4%	30.7%	15.0%	15.5%	<0.01
Good recovery	70.9%	65.4%	56.4%	57.7%	62.9%	<0.05
Actual surgery interval						
Unadjusted						
Mortality	12.6%	11.9%	15.1%	2.4%	6.5%	<0.05
Good recovery	69.9%	69.7%	61.6%	80.0%	63.2%	0.052
Adjusted						
Mortality	13.6%	15.3%	18.3%	3.4%	6.3%	<0.005
Good recovery	75.1%	71.8%	60.9%	78.2%	70.4%	NS

Adjusted refers to data controlled for differences in prognostic variables between the groups (see "Subjects and Methods").

tients. Hypervolemia combined with induced hypertension was used in 10%.

Preoperative and postoperative management routines were consistent with practices in other geographic regions, except that intracranial pressure monitoring was more likely to be used in North American centers (11.9% versus 2.8%, $p<0.001$). Ventricular cerebrospinal fluid drainage, a practice commonly used postoperatively in Japan (32% of patients), was not used as frequently in North America (6%).

TABLE 9. Overall Outcome by Admission Level of Consciousness and Planned Surgical Interval

Admission level of consciousness	Planned surgical interval (days)	Good recovery		Moderately disabled		Severely disabled		Vegetative survival		Dead		Total
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Alert	0–3	115	79.3	13	9.0	2	1.4	1	0.7	14	9.7	145
	4–6	33	75.0	3	6.8	3	6.8	0	0.0	5	11.4	4
	7–10	58	70.7	12	14.6	3	3.7	0	0.0	9	11.0	82
	11–14	42	68.9	4	6.6	4	6.6	1	1.6	10	16.4	61
	15–32	8	72.7	1	9.1	0	0.0	1	9.1	1	9.1	11
	None	6	50.0	1	8.3	1	8.3	0	0.0	4	33.3	12
Drowsy	0–3	52	67.5	10	13.0	4	5.2	0	0.0	11	14.3	77
	4–6	14	63.6	3	13.6	3	13.6	0	0.0	2	9.1	22
	7–10	29	47.5	3	4.9	3	4.9	2	3.3	24	39.3	61
	11–14	31	47.0	17	25.8	2	3.0	1	1.5	15	22.7	66
	15–32	14	63.6	0	0.0	5	22.7	0	0.0	3	13.6	22
	None	2	16.7	1	8.3	2	16.7	0	0.0	7	58.3	12
Stuporous	0–3	14	46.7	5	16.7	3	10.0	1	3.3	7	23.3	30
	4–6	2	28.6	1	14.3	1	14.3	1	4.3	2	28.6	7
	7–10	3	25.0	2	16.7	3	25.0	1	8.3	3	25.0	12
	11–14	9	47.4	4	21.1	1	5.3	0	0.0	5	26.3	19
	15–32	6	50.0	0	0.0	1	8.3	2	16.7	3	25.0	12
	None	1	14.3	0	0.0	1	14.3	1	14.3	4	57.1	7
Comatose	0–3	1	11.1	2	22.2	2	22.2	0	0.0	4	44.4	9
	4–6	0	0.0	2	50.0	0	0.0	0	0.0	2	50.0	4
	7–10	3	37.5	1	12.5	0	0.0	1	12.5	3	37.5	8
	11–14	3	37.5	1	12.5	0	0.0	2	25.0	2	25.0	8
	15–32	2	25.0	0	0.0	2	25.0	0	0.0	4	50.0	8
	None	3	9.1	0	0.0	1	3.0	0	0.0	29	87.9	33

Table 3 gives the planned versus actual surgery intervals for the North American subgroup. One third (33.9%) of patients had early surgery planned for within the first 3 days from hemorrhage, whereas 48% had surgery planned for after the first week. Compared with other regions (particularly Japan, where 75% of patients had surgery planned for days 0–3), North American surgeons were more likely to plan for surgery after the first week. Those patients who were planned for surgery on days 0–3 were more likely to undergo actual surgery in that interval than those planned for later intervals. Those patients who had surgery planned for after day 7 frequently had surgery delayed or not performed because of neurological deterioration or death. Overall, 63.1% actually had surgery during the planned interval.

Preoperative and postoperative neurological and medical complications were reported more frequently in North American patients (Tables 4 and 5). Focal ischemic deficits (predominantly from symptomatic vasospasm), brain swelling, and hydrocephalus were reported in 34.8%, 13.6%, and 18.5% of North American patients, respectively. Several medical complications, including pulmonary disorders and blood pressure abnormalities, were reported more frequently in North American centers. This observation may reflect more intensive monitoring and reporting in these patients or may be a complication of the more aggressive medical interventions outlined previously.

Despite the increase in neurological and medical complications reported, the mortality rate of patients treated in North American centers was better than that in other regions (Table 6). The mortality rate at 6 months, adjusted for baseline prognostic variables, was significantly lower in North American centers (p=0.0003). Comparison of unadjusted Glasgow Outcome Scale scores shows similar proportions of patients attaining good recovery at follow-up. Caution should be used in interpreting the unadjusted data, however.

Table 7 presents the primary causes of death or disability listed by planned surgical interval. Of the 64 patients initially deemed to be unfit for surgery, 69% died, most as a direct consequence of the initial hemorrhage. In the patients planned for surgery on days 15–32, morbidity and mortality from direct effects was 18.9%. In the other planned surgical intervals, morbidity and mortality from direct effects averaged 9–10%. Although mortality from surgical complications was higher in the groups of patients planned for surgery before day 10, morbidity from surgical complications was higher in patients planned for days 11–32. As with the overall study, death and disability from vasospasm was higher in the group planned for surgery on days 0–6, whereas those planned for late intervals (after day 14) were more likely to succumb to rebleeding.

In terms of overall outcome (Table 8), mortality was significantly worse in the group of patients planned for surgery in the day 7–10 interval. Mortality in patients planned for surgery during days 0–3 was 15% and was equivalent to that of the later planned surgical intervals. The percentage of patients achieving good recovery at 6 months, however, was significantly better in those patients planned for surgery in days 0–3. Of those patients actually undergoing surgery, the results were best in the days 11–14 interval, consistent with reports from other surgical series[12,13] and reflecting the attrition and selection bias that occurs during days 0–10.

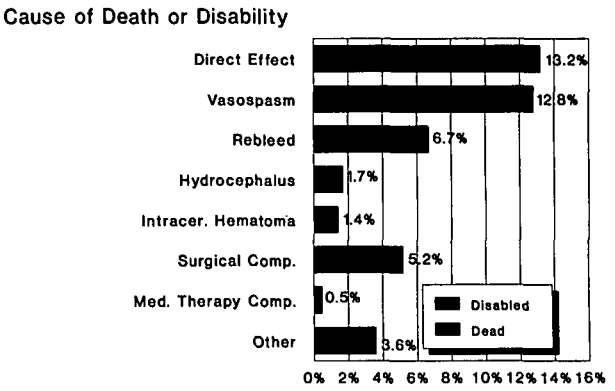

FIGURE 1. *Bar graph depicting the distribution of death or disability (defined as any Glasgow Outcome Score other than good recovery or death) at 6 months by primary cause in patients with aneurysmal subarachnoid hemorrhage admitted to North American centers of the International Cooperative Study on the Timing of Aneurysm Surgery. Percentages are of the total 772 North American patients.*

With regard to subgroups that might benefit from a particular surgical timing strategy, Table 9 shows outcomes by planned surgical interval and admission level of consciousness. Alert patients generally did well regardless of the planned surgical interval, but drowsy patients had better outcomes if surgery was planned before day 6 or after day 14. Comatose patients with surgery planned for after the first week generally had better outcomes, although the mortality was high in all planned surgical intervals for this group of patients.

Discussion

This study describes several key aspects of the admission characteristics, elements of neurosurgical practice, and results of treatment in a large cohort of patients with ruptured aneurysms admitted to several major neurosurgical referral centers in North America from 1980 through 1983. As such, it represents a historical blueprint of the results of SAH treatment before the widespread use of interventions for cerebral vasospasm, such as intentional hypervolemia and induced hypertension[14] or calcium antagonist drugs.[15] Without an effective treatment for vasospasm, patients were more likely to die of or to be disabled by this disorder than by any other cause, except for direct effects of the initial hemorrhage (Figure 1). Rebleeding also remained a major prob-

lem, perhaps related to the prevailing philosophy favoring delayed surgery at the time.

In contrast to the results of the overall study, overall good recovery, adjusted for prognostic factors and center variability, was better in the group planned for surgery during days 0–3 than that planned for surgery during days 11–32 ($p<0.01$, χ^2 test). Results were worst when surgery was planned for the days 7–10 period, which is now recognized as the period of greatest risk for angiographic and symptomatic cerebral vasospasm. While mortality from surgical complications was slightly reduced in those assigned the delayed strategy, surgical morbidity was not. With potentially effective strategies for managing vasospasm now available,[16] there is evidence that more North American neurosurgeons are adopting a preference for early surgery.[17]

As a subset of a much larger, international epidemiological survey, the results of treatment in North American neurosurgical centers compared quite favorably with results reported from other regions.[18,19] As reported previously, the North American and Japanese 6-month mortality and good recovery rates were virtually identical (22% and 58%, respectively) and were superior to results reported from other regions.[6]

The results of this trial provide impetus for further research into treatment for SAH patients. It was discouraging to discover that although 75% of patients with recently ruptured aneurysms were admitted in an alert or drowsy state with no motor or speech deficits, only 58% were living independently without a major neurological deficit 6 months later. Advances in the management of rebleeding and vasospasm, complications that occur frequently while patients are already hospitalized, should translate into immediately tangible improvements in overall outcome. As both these phenomena occur soon after the initial hemorrhage, it behooves primary care and emergency physicians to become more adept at early diagnosis and rapid referral of SAH patients if the devastating consequences of rebleeding and vasospasm are to be prevented.

Appendix A

North American Participants in International Cooperative Study on the Timing of Aneurysm Surgery

Center	Reporting Investigator
Canada	
University of Alberta, Edmonton, Alberta	B. Weir
University of Toronto, Toronto, Ontario	W.S. Tucker
University of Western Ontario, London, Ontario	S.J. Peerless
United States	
Albert Einstein College of Medicine, Bronx, N.Y.	H. Wisoff
Barrow Neurological Institute, Phoenix, Ariz.	L.P. Carter
Case Western Institute, Cleveland, Ohio	R. Ratcheson R. Spetzler
Duke University Medical Center, Durham, N.C.	A. Friedman
Indiana University, Indianapolis, Ind.	R. Campbell
Louisiana State University, New Orleans, La.	R. Smith
Massachusetts General, Boston, Mass.	R. Heros
Mayfield Neurological Institute, Cincinnati, Ohio	J. Tew
New York University Medical Center, New York, N.Y.	E. Flamm
Ohio State University, Columbus, Ohio	C. Miller
Pennsylvania Hospital, Philadelphia, Pa.	F. Simeone
University of California Medical Center, San Diego, Calif.	L.F. Marshall
University of California, San Francisco, Calif.	L. Pitts
University of Florida, Gainesville, Fla.	A. Day
University of Iowa, Iowa City, Iowa	N.F. Kassell
University of Minnesota, Minneapolis, Minn.	S.N. Chou
University of Michigan, Ann Arbor, Michigan	J. Hoff
University of Mississippi, Jackson, Miss.	R. Smith
University of Pittsburgh, Pittsburgh, Pa.	H. Yonas
University of Southern California, Los Angeles, Calif.	S. Ginnotta
University of Tennessee, Memphis, Tenn.	M. Ray
University of Texas Health Science Center, Dallas, Tex.	D. Samson
Vanderbilt University, Nashville, Tenn.	W. Meacham
Washington University School of Medicine, St. Louis, Mo.	R. Grubb

Appendix B

Advisory Committee

Harold P. Adams Jr., MD, Professor of Neurology, University of Iowa; Charles G. Drake, MD, Professor of Neurosurgery, University of Western Ontario; Mark L. Dyken Jr., MD, Professor of Neurology, Indiana University; Eugene S. Flamm, MD, Professor of Neurosurgery, University of Pennsylvania; Ralph F. Frankowski, PhD, Professor of Biometry, University of Texas; John A. Jane, MD, PhD, Professor of Neurosurgery, University of Virginia; John F. Kurtzke, MD, Professor of Neurology, Georgetown University; S.J. Peerless, MD, Professor of Neurosurgery, University of Western Ontario; A.L. Sahs, MD (deceased), Professor Emeritus of Neurology, University of Iowa.

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