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Impact of Medical Treatment on the Outcome of Patients After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—The rationale behind early aneurysm surgery in patients with subarachnoid hemorrhage (SAH) is the prevention of rebleeding as early as possible after SAH. In addition, by clipping the aneurysm as early as possible, one can apply treatment for cerebral ischemia more vigorously (induced hypertension) without the risk of rebleeding. Hypervolemic hemodilution is now a well-accepted treatment for delayed cerebral ischemia. We compared the prospectively collected clinical data and outcome of patients admitted to the intensive care unit in the period 1977 to 1982 with those of patients admitted in the period 1989 to 1992 to measure the effect of the change in medical management procedures on patients admitted in our hospital with SAH.

Methods—We studied 348 patients admitted within 72 hours after aneurysmal SAH. Patients with negative angiography results and those in whom death appeared imminent on admission were excluded. The first group (group A) consisted of 176 consecutive patients admitted from 1977 through 1982. Maximum daily fluid intake was 1.5 to 2 L. Hyponatremia was treated with fluid restriction (<1 L/24 h). Antihypertensive treatment with diuretic agents was given if diastolic blood pressure was >110 mm Hg. Patients in the second group (172 consecutive patients; group B) were admitted from 1989 through 1992. Daily fluid intake was at least 3 L, unless cardiac failure occurred. Diuretic agents and antihypertensive medications were avoided. Cerebral ischemia was treated with vigorous plasma volume expansion under intermittent monitoring of pulmonary wedge pressure, cardiac output, and arterial blood pressure, aiming for a hematocrit of 0.29 to 0.33. Aneurysm surgery was planned for day 12.

Results—Patients admitted in group B had less favorable characteristics for the development of cerebral ischemia and for good outcome when compared with patients in group A. Despite this, we found a significant decrease in the frequency of delayed cerebral ischemia in patients of group B treated with tranexamic acid ($P=0.00005$ by log rank test) and significantly improved outcomes among patients with delayed cerebral ischemia ($P=0.006$ by χ^2 test) and among patients with deterioration from hydrocephalus ($P=0.001$ by χ^2 test). This resulted in a significant improvement of the overall outcome of patients in group B when compared with those in group A ($P=0.006$ by χ^2 test). The major cause of death in group B was rebleeding ($P=0.011$ by χ^2 test).

Conclusions—We conclude that the outcome in our patients with aneurysmal SAH was improved but that rebleeding remains a major cause of death. Patient outcome can be further improved if we can increase the efficacy of preventive measures against rebleeding by performing early aneurysm surgery. (*Stroke*. 1998;29:924-930.)

Key Words: hemodilution ∎ intracranial aneurysm ∎ outcome ∎ subarachnoid hemorrhage

Treatment of SAH is aimed at prevention of rebleeding through clipping of the aneurysm and at prevention and treatment of cerebral ischemia and hydrocephalus. Many articles have been published on the management of patients after SAH from a ruptured intracranial aneurysm, and almost all reported either results of a study concerning drug efficacy[1,2] or results of studies concerning early versus delayed aneurysm surgery. More and more neurosurgeons rely on early aneurysm surgery rather than delayed surgery for the prevention of rebleeding after aneurysmal SAH.[3–12] The rationale behind early aneurysm surgery is that by clipping the aneurysm as early as possible, one can apply treatment for cerebral ischemia more vigorously (for example, induced hypertension) without the risk of a rebleed. However, in most studies early aneurysm surgery failed to improve outcome when compared with delayed surgery, probably because of an increase in the frequency of cerebral ischemia.[5–12] However, two studies reported a beneficial effect of early surgery.[3,4] In contrast to the previous studies,[5–12] in these two studies[3,4] prophylactic hypervolemic therapy was applied during the postoperative period. In addition, the favorable effects of hypervolemic hemodilution on cerebral perfusion have been reported in experimental studies[13,14] and on cerebral ischemia in patients with SAH.[15–21] Until recently, early aneurysm

surgery was not performed in our center. On the other hand, medical treatment of patients with SAH was gradually changing: increase in daily fluid intake, immediate treatment of hydrocephalus and high CSF pressure, introduction of treatment of cerebral ischemia with hypervolemic hemodilution, and prescription of nimodipine. Therefore, we have the opportunity to compare the prospectively collected clinical data and outcome of patients admitted to the ICU in the period 1977 to 1982 with those of patients admitted in the period 1989 to 1992. We did not restrict our study to patients who were fit enough to undergo aneurysm surgery, and our objective was to measure the effect of the change in the whole package of medical management in all patients admitted to our hospital with SAH.

Subjects and Methods

From November 1977 through December 1992 we studied 779 consecutive patients with SAH who were admitted to the ICU. All patients had clinical features of SAH and were admitted within 72 hours after the bleed. SAH was confirmed by CT, revealing distribution of subarachnoid blood compatible with aneurysmal hemorrhage, or when the CT scan revealed no blood, by spectrophotometric analysis of the CSF. If the patient had a motor score of 3 on the GCS and negative pupillary reflexes on admission, or if the motor score on admission was ≤2 and the level of consciousness did not improve within 72 hours after admission, the patient was excluded from the study (80 patients). In addition, patients with negative angiograms (39 patients) were not entered in the study. Between 1977 and 1982, medical treatment remained unchanged. From 1983 until 1989, medical treatment of patients with SAH was gradually changing (for example, increase in daily fluid intake, immediate treatment of hydrocephalus, treatment of cerebral ischemia with hypervolemic hemodilution, and prescription of nimodipine). From 1989 onward, medical treatment remained grossly unchanged. Therefore, from the remaining 660 patients, we included those admitted between 1977 and 1982 (n=176) and between 1989 and 1992 (n=172).

CT scanning was performed on admission (initial CT scan). The amount of blood in each of the 10 cisterns was graded, on a scale of 0 to 3, separately for each of the 10 cisterns (maximum sum score of 30).[22] A sum score of 18 or higher was regarded as a "high cisternal blood score." Similarly, intraventricular blood was graded separately for each of the four ventricles (maximum sum score of 12). Because a ventricular score of 1 reflects sedimentation of red blood cells in the ventricle, we considered relevant only a score of >1 for at least one of the four ventricles, and we referred only to this as "presence of intraventricular blood."

All patients were kept in the ICU during the first 28 days or until death or aneurysm surgery. The level of consciousness was assessed by means of the 14-point GCS.[23] When deterioration of the patient's clinical condition occurred, physical examination (and CT scan if possible) was repeated. Hydrocephalus detected by CT on admission was referred to as "hydrocephalus on the initial CT." Hydrocephalus is defined as the bicaudate index (width of the frontal horns at the level of the foramina of Monro, divided by the corresponding diameter of the brain) on the CT exceeding the 95th percentile for age. The upper limits were as follows: <36 years of age, 0.16; 36 to 45 years, 0.17; 46 to 55 years, 0.18; 56 to 65 years, 0.19; 66 to 75 years, 0.20; and 76 to 85 years, 0.21.[24,25] Clinical events occurring

during the observation period were defined as follows: (1) deterioration from hydrocephalus was defined as deterioration of the level of consciousness with no detectable cause other than hydrocephalus confirmed by a repeat CT; (2) probable delayed ischemia was gradual development of focal neurological signs with or without deterioration of the level of consciousness, without confirmation by CT or autopsy; (3) definite cerebral ischemia was defined as development of focal neurological signs or deterioration of the level of consciousness, or both, with CT or autopsy evidence of cerebral infarction; (4) probable rebleeding was sudden deterioration of the level of consciousness and death, without CT confirmation or if autopsy was refused; and (5) definite rebleeding was defined as sudden deterioration of the level of consciousness, with or without focal signs, with an increase in the amount of blood on a repeat CT or at autopsy when compared with a previous CT scan. In the analysis we counted definite and probable cerebral ischemia as cerebral ischemia and definite and probable rebleeding as rebleeding.

In the first period (November 1977 through December 1982, group A), the patients (n=176) were enrolled in a multicenter trial (centers in the United Kingdom and the Netherlands were involved) on the effect of tranexamic acid.[26] These patients were randomized for tranexamic acid: 89 patients received placebo treatment (group A₁) and 87 patients were treated with tranexamic acid for 28 days or until aneurysm surgery (6 g/d intravenously in the first week and 4 g/d intravenously or 6 g/d orally in the next 3 weeks, group A₂). Maximum daily fluid intake was between 1.5 and 2 L. Hyponatremia was treated with fluid restriction (<1 L/24 h) under the assumption, now proved incorrect, that hyponatremia was caused by the syndrome of inappropriate secretion of antidiuretic hormone.[27–30] We did not apply preventive measures against cerebral ischemia or hypervolemic hemodilution. Antihypertensive treatment with diuretic agents was given if diastolic blood pressure was >110 mm Hg. External ventricular drainage was performed when the patient deteriorated from hydrocephalus, we were reluctant to insert a ventricular catheter when the clinical condition of the patient deteriorated mildly. We preferred external drainage to internal shunt in the first 2 weeks after SAH.

From 1989 through 1992 all 172 patients (group B) were treated with tranexamic acid and nimodipine (6×60 mg/d orally or 2 mg/h intravenously) during the first 21 days or until their operations.[1,2] As preventive measure for cerebral ischemia, daily fluid intake was at least 3 L unless cardiac failure occurred.[27–30] Fludrocortisone (2×0.2 mg/d) was administered as a preventive measure against hyponatremia. When hyponatremia did occur, sodium chloride was administered. Diuretic agents were avoided. Antihypertensive medication was not given unless the patient was on this medication on admission. In the absence of a hematoma with mass effect and if blood did not completely fill the third and fourth ventricles, we treated hydrocephalus by means of serial lumbar puncture or external lumbar CSF drainage. If hydrocephalus persisted or if a contraindication for lumbar puncture existed, an external ventricular catheter was inserted. We preferred external CSF drainage to internal shunt during the first 2 weeks after the bleed for obvious reasons. When cerebral ischemia occurred, it was treated with vigorous plasma volume expansion under intermittent monitoring of pulmonary wedge pressure, cardiac output, pulmonary arterial pressure, systemic vascular resistance (by means of a Swan-Ganz catheter), and systemic arterial blood pressure, aiming at a hematocrit of 0.29 to 0.33.[13–21]

Angiography was performed depending on the patients' clinical condition. An aneurysm was confirmed either by angiography or by autopsy in 130 of 176 (74%) patients in group A and in 142 of 172 (83%) patients in group B (Table 1). In the remaining 76 of the 348 (22%) patients aneurysm rupture was considered highly probable because of the extravasation of blood in the frontal interhemispheric, suprasellar, or Sylvian cisterns without evidence of other causes of SAH. Aneurysm clipping was planned for day 12 in all groups. All surviving patients had a follow-up for at least 3 months after SAH. They visited the outpatient clinic or were interviewed by means of a written questionnaire. Outcome was assessed by means of the 5-point GOS.[31] We reduced the GOS to three categories: dead (GOS

TABLE 1.   Characteristics of 348 Patients With Aneurysmal SAH

	Group A 1977–1982 (n=176)		Group B 1989–1992 (n=172)	
	No.	%	No.	%
Sex				
Male	68	39	57	33
Female	108	61	115	67
Mean age, y	52.1		51.5	
≤40	38	22	42	24
41–60	80	45	81	47
>60	58	33	49	28
Lost of consciousness at ictus, n	88	52	101	59
Duration of loss of consciousness at ictus, h				
<1	47	53	61	60
1–8	21	24	23	23
9–24	5	6	4	4
25–72	12	14	0	0
Unknown	3	3	13	13
Sum score of Glasgow Coma Scale				
≤12	61	35	65	38
>12	115	65	107	62
Sum score of cisternal blood on initial CT				
<18	153	87*	71	41.5
18–30	23	13*	100	58.0
Not graded	0	0	1	0.5
Ventricular blood, n				
Present	43	24†	60	35
Absent	133	75†	110	64
Not graded	0	0	2	1
Aneurysm confirmed, n	130	74	142	83
Carotid artery	51	39‡	35	25
Middle cerebral artery	19	15‡	37	26
Anterior cerebral artery	52	40‡	46	32
Posterior circulation	8	6‡	23	16
Unknown (multiple aneurysm)	0	0‡	1	1
Hydrocephalus on initial CT, n	35	20§	57	33

n indicates number of patients. Significantly different from number than patients in group A by χ^2-test: $*\chi^2=78.165$, $P<0.000001$; $†\chi^2=4.88$, $P=0.027$; $‡\chi^2=16.891$, $P=0.002$; and $§\chi^2=10.685$, $P=0.001$.

score of 1), dependent (GOS score of 2 or 3), and independent (GOS score of 4 or 5).

Differences in frequency of entry characteristics, outcome, and cause of death between groups were assessed with the two-sided χ^2 test. Because patients with a GCS score of 13 (14-point GCS) were either drowsy or disorientated without a decrease in the motor score, we chose a GCS score of 12 as the breakpoint for the analysis (Figure 1). Differences in first-occurring cerebral events (deterioration from hydrocephalus, delayed cerebral ischemia, and rebleeding) and differences in time-dependent medical treatments (aneurysm surgery, external CSF drainage, internal CSF shunt) between groups were analyzed by plotting Kaplan-Meier survivor function estimates against time. Univariate analysis, stratified by one variable at a time, was performed with the log

rank test.[32,33] We stress that in the analysis of outcome at 3 months (as presented in Figure 3), calculations of the proportion of patients with first-occurring cerebral complication were done with simple arithmetic. On the other hand, in the Kaplan-Meier plots as presented in Figure 1, calculations of the proportion of patients with first-occurring cerebral complication were performed by means of the estimation of the survivor function.[32] One must bear in mind that there is a difference in the results of the calculated proportion of patients between these two methods due to, among others, the censoring mechanism of survival analysis.[34]

Results

Characteristics of all patients are presented in Table 1. Patients in group A exhibited less cisternal ($P<0.000001$ by χ^2 test) and less ventricular blood on the initial CT scan compared with patients in group B. The proportion of patients with an aneurysm of the posterior circulation was significantly higher in group B than in group A. Hydrocephalus on the initial CT was found in a significantly greater proportion in patients of group B than in group A. The proportion of patients free from deterioration from hydrocephalus was lower in group B than in group A_1 ($P<0.000001$ by log rank test) and group A_2 ($P=0.00003$ by log rank test; Figure 1). In addition, the proportion of patients free from deterioration from hydrocephalus was lower in group A_2 than group A_1 ($P=0.0044$ by log rank test; Figure 1). In patients treated with tranexamic acid, cerebral ischemia developed less often in group B compared with group A_2 ($P=0.00005$ by log rank test; Figure 1). The difference in the development of cerebral ischemia between group A_1 and group A_2 was not statistically significant. The proportion of patients free from rebleeding was lower in group A_2 ($P=0.0009$ by log rank test) and group B ($P=0.0049$ by log rank test) than in group A_1 (Figure 1). Aneurysm surgery was performed more frequently in group B than in group A_1 ($P=0.0290$ by log rank test) and group A_2 ($P=0.000005$ by log rank test; Figure 1). The proportion of patients free from aneurysm surgery in group A_1 was lower than that in group A_2 ($P=0.0341$ by log rank test; Figure 1). The proportions of patients who received CSF drainage and internal ventricular shunting are summarized in Figure 2. External CSF drainage was performed more frequently in group B than group A_1 ($P=0.0016$ by log rank test) and group A_2 ($P=0.0006$ by log rank test). No differences in the frequency of internal ventricular shunts between groups were seen.

Figure 3 shows the outcome at 3 months of all 348 patients. In patients without complications, outcome between group A and group B was not significantly different. Mortality in patients in whom rebleeding occurred as a first cerebral complication was slightly higher in group B than group A, but the difference was not statistically significant. Outcome in patients with deterioration from hydrocephalus in group B was significantly better when compared with that of patients in group A ($P=0.001$ by χ^2 test). This difference is caused by a decrease in the proportion of patients with dependent outcome and a decrease in the mortality of patients with deterioration from hydrocephalus in group B. Among patients with cerebral ischemia, outcome was also significantly better in
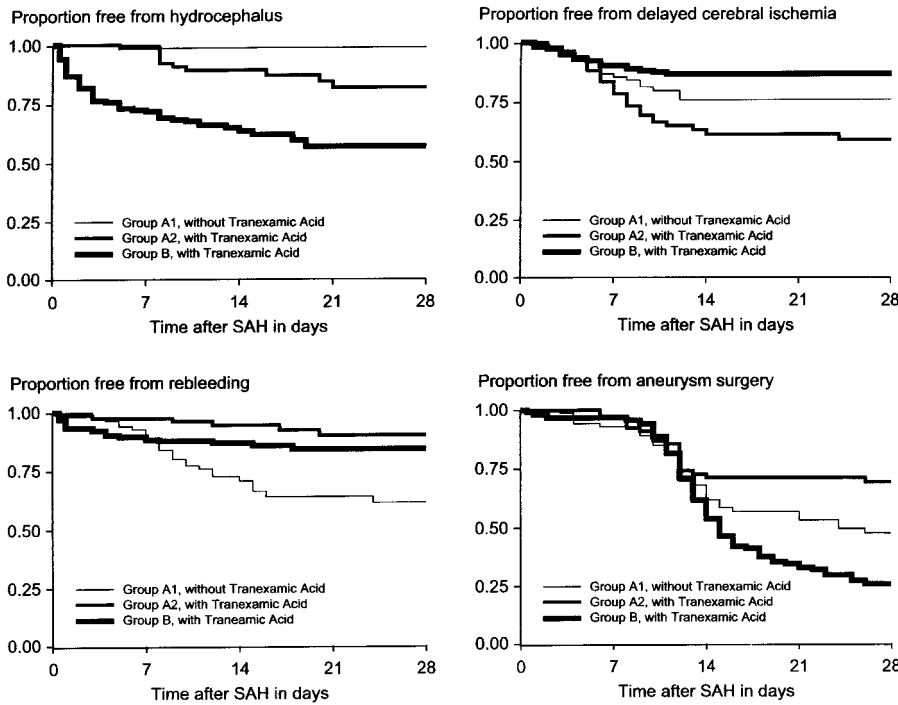
Figure 1. Plots of Kaplan-Meier survival function estimates against time on the first-occurring cerebral complication after the initial SAH and on aneurysm surgery in 348 patients.

group B than in group A ($P=0.006$ by χ^2 test). This change was caused by a decrease in the mortality of patients with cerebral ischemia in group B. As a consequence, overall outcome in group B was significantly better than that in group A ($P=0.006$ by χ^2 test).

In group A, both cerebral ischemia and rebleeding are major causes of death (Table 2). In group B, cerebral ischemia as cause of death occurred significantly less often than in group A ($P=0.033$ by χ^2 test). In contrast, rebleeding as cause of death occurred significantly more often in group B than in group A ($P=0.011$ by χ^2 test).

Discussion

Patients in group B had more unfavorable prognostic factors for cerebral ischemia (such as amount of cisternal blood on the initial CT scan and the presence of ventricular blood) and for good outcome (amount of cisternal blood and aneurysm of the posterior circulation) than patients in group A (Table 1). This is probably the result of a change in the referral behavior of consultants in the region of our hospital. Apparently, more patients with severe bleeding were referred to our hospital from 1989 through 1992 (group B).

The high frequency of hydrocephalus demonstrated on the admission CT scan and the high frequency of deterioration from hydrocephalus in group B compared with those in group A are probably the result of the higher frequency of patients with high amounts of cisternal blood and a higher frequency of the presence of ventricular blood in group B (Figure 1). Both are prognostic factors for the development of deterioration from hydrocephalus.[35,36] Improvement of outcome in patients with hydrocephalus is obviously the result of a change in the treatment of hydrocephalus. In group A patients, we were reluctant to insert a ventricular catheter when the clinical condition of the patient deteriorated mildly. In contrast, we switched to lumbar puncture and lumbar external drainage in group B, and we initiated external CSF drainage more frequently than in group A (Figure 3). Despite this, the need for permanent internal shunting was not different between group A_2 and group B; both groups were treated with tranexamic acid (Figure 3), a risk factor for deterioration from hydrocephalus.[35,36] It is known that external CSF drainage may precipitate rebleeding.[37,38] Despite this, there was a significant decrease in the proportion of death and
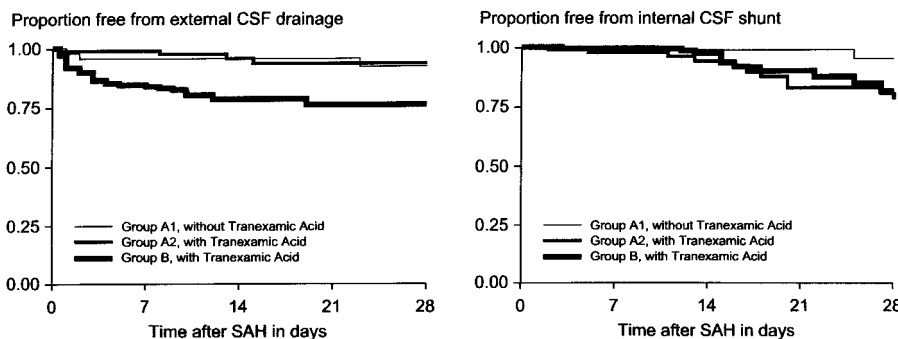

Figure 2. Plots of Kaplan-Meier survival function estimates against time on CSF drainage after the initial SAH in 348 patients.
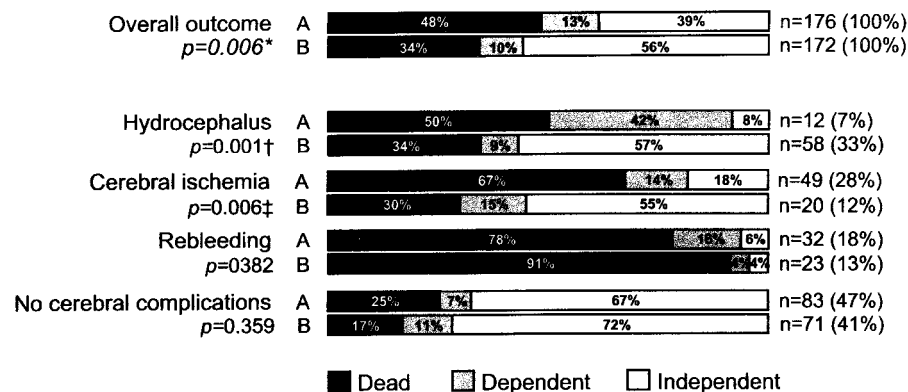
Figure 3. Bar graph showing the outcome at 3 months in 348 patients with SAH, stratified by first-occurring cerebral complication after SAH.

Group A is significantly different from number than group B by χ^2-test:

* $\chi^2 = 10.330, p=0.006$

† $\chi^2 = 13.073, p=0.001$

‡ $\chi^2 = 10.085, p=0.006$

dependent patients in those patients with deterioration from hydrocephalus in group B compared with similar patients in group A, which resulted from our change in strategy ($P=0.006$ by χ^2 test; Figure 3).

Daily fluid intake in group B was much higher than that in group A, and fluid restriction in hyponatremic patients was omitted in group B in contrast to group A. In addition, cerebral ischemia in group B was treated with hypervolemic hemodilution (aiming for a hematocrit of about 0.30) under invasive monitoring of cardiac output, pulmonary wedge pressure, pulmonary arterial pressure, and systemic blood pressure. The idea was to optimize the low shear-rate viscosity of the whole blood and to ensure adequate cerebral perfusion pressure in order to restore the regional cerebral blood flow in perfusion areas beyond the vaso-spastic vessels.[13–21] Although patients in group B were treated with tranexamic acid, and despite the fact that this treatment may precipitate cerebral ischemia in patients with aneurysmal SAH, the occurrence of cerebral ischemia in group B was significantly lower than that in group A_2 ($P=0.00005$ by log rank test) and slightly lower than that

of group A_1 (Figure 2). Moreover, outcome at 3 months for patients in group B was significantly better than that of group A (Figure 3). The decrease in the occurrence of cerebral ischemia in group B can probably be attributed to the high daily fluid intake and the well-accepted beneficial effect of hypervolemic hemodilution.[13–21]

Although the characteristics of the patients in group B were worse than those of group A patients with regard to the prognostic factors for the occurrence of cerebral ischemia and bad outcome,[39–44] the decrease in the frequency and mortality rate of cerebral ischemia and the improved results of hydrocephalus treatment led to an increase in the proportion of patients fit for aneurysm surgery at the end of the second week after the initial bleed. As a result, overall outcome improved significantly (Figure 3). However, rebleeding became a more frequent cause of death in group B when compared with group A (Table 2).

An article on a study performed from 1977 through 1981 reported good outcome in patients with SAH (46%), similar to that in group A.[45] Other studies, performed after 1985, have reported a similar proportion (56%) of good outcome when compared with group B.[5] Others have reported a better result (71% to 87% good outcome) than that in group B.[43,46–50] Patients included in the latter study were those admitted to a neurosurgical unit. Consequently, most of these patients were in a fair clinical condition, fit for surgery. This probably explains the difference in outcome when compared with group B. Improved outcome, when corrected for prognostic factors for bad outcome,[39,40,42,43] is probably the result of improved management: operative technique, timing of aneurysm surgery, or improved medical treatment. In a retrospective study, it was reported that outcome improved after treatment with hypervolemic hemodilution was initiated.[48] On the other hand, nonrandomized trials on the timing of aneurysm surgery failed to show a significant difference between early and delayed surgery. Although early surgery lowered

TABLE 2. Cause of Death in 144 Patients With Aneurysmal SAH

Cause of Death	Group A 1977–1982 (n=85)		Group B 1989–1992 (n=59)	
	No.	%	No.	%
Initial bleed	1	1	4	7
Cerebral ischemia	22	26	6*	10
Rebleeding	31	37	35†	59
Hydrocephalus	6	7	0	0
Other‡	25	29	14	24

Significantly different from number than patients in group A by χ^2 test:
*$\chi^2=4.53$, $P=0.033$; †$\chi^2=6.43$, $P=0.011$.

‡Other causes of death were pulmonary embolism, neurogenic pulmonary edema, septic shock, and operative complications.

the rebleeding rate significantly, this beneficial effect was negated by a substantial increase in postoperative cerebral ischemia.[5–12] In contrast, a prospectively performed randomized study[3] reported an improved outcome after early surgery (0 to 3 days) compared with that after delayed surgery (>8 days after SAH) (96% [25 of 26 patients] versus 77% [22 of 28 patients]). However, the difference did not reach statistical significance because of the small numbers of patients included.

We conclude that outcome in our patients with aneurysmal SAH was improved in the course of time as the result of a change in the medical treatment strategy of these patients, which led to an improved outcome in patients with cerebral ischemia and those with deterioration from hydrocephalus. On the other hand, rebleeding remains a major cause of death. A further improvement in the outcome of these patients is possible if we can increase the efficacy of preventive measures against rebleeding by performing early aneurysm surgery.

Acknowledgments

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