Initial and Recurrent Bleeding Are the Major Causes of Death Following Subarachnoid Hemorrhage

Joseph P. Broderick, MD; Thomas G. Brott, MD; John E. Duldner, MD; Thomas Tomsick, MD; Alan Leach, MS

Background and Purpose  The goal of this study was to determine the causes of mortality and morbidity after subarachnoid hemorrhage.

Methods  We identified all first-ever spontaneous subarachnoid hemorrhages that occurred in the nearly 1.3 million population of greater Cincinnati during 1988.

Results  Thirty-day mortality for subarachnoid hemorrhage was 45% (36 of 80 cases). Of the 36 deaths, 22 (61%) died within 2 days of onset; 21 of these deaths were due to the initial hemorrhage, and one death was due to rebleeding documented at autopsy. Nineteen of the remaining 14 deaths after day 2 were caused by the initial hemorrhage (2 cases) or rebleeding (7 cases). Volume of subarachnoid hemorrhage was a powerful predictor of 30-day mortality (P=0.001). Only 3 of the 29 patients with a volume of subarachnoid hemorrhage of 15 cm³ or less died before 30 days. Two of these 3 patients died from documented rebleeding; the third had 87 cm³ of additional intraventricular hemorrhage. Delayed arterial vasospasm contributed to only 2 of all 36 deaths.

Conclusions  Most deaths after subarachnoid hemorrhage occur very rapidly and are due to the initial hemorrhage. Rebleeding is the most important preventable cause of death in hospitalized patients. In a large representative metropolitan population, delayed arterial vasospasm plays a very minor role in mortality caused by subarachnoid hemorrhage. (Stroke, 1994;25:1342-1347.)

Key Words  • subarachnoid hemorrhage  • mortality

Surgical and medical treatment studies of subarachnoid hemorrhage have reported that vasospasm and rebleeding are the major causes of 30-day mortality and morbidity after subarachnoid hemorrhage. These treatment studies almost always exclude the most moribund patients and patients who die before reaching the hospital. Yet, only studies that examine the outcome of all patients in a large, well-defined population can accurately determine the most important causes of early death and morbidity after subarachnoid hemorrhage. This information is necessary to determine the most effective public health strategies for decreasing the morbidity and mortality associated with this deadly disease.

The present study examines the causes of morbidity and mortality associated with all cases of subarachnoid hemorrhage that occurred in the nearly 1.3 million population of greater Cincinnati during 1988.

Subjects and Methods

All first-ever spontaneous subarachnoid hemorrhages that occurred in greater Cincinnati during 1988 were identified as previously reported.6 Inclusion in the study required that at the onset of hemorrhage the patient resided in the five-county region, as determined by zip code, that the onset of the subarachnoid hemorrhage occurred during 1988, and that the patient met the criteria for subarachnoid hemorrhage. Subarachnoid hemorrhage was defined as blood in the subarachnoid spaces, not caused by trauma, detected by computed tomography (CT) scanning or at autopsy, or as a clinical history and examination consistent with subarachnoid hemorrhage (sudden onset of severe headache or change in level of consciousness) with xanthochromia and many red cells in the cerebrospinal fluid.

The medical record systems reviewed included those of all 20 acute care hospitals and five coroners' offices in the five-county region. Three of these hospitals can be characterized as referral centers for aneurysmal subarachnoid hemorrhage, 15 are community hospitals, 1 is a Veterans Hospital, and 1 is a tertiary-referral children's hospital. Patients with subarachnoid hemorrhage who were referred from outside of the five-county region were excluded.

The abstracted clinical data and all available CT and magnetic resonance imaging films for each case were evaluated by a neurologist. Selected films were also evaluated by a neuroradiologist. We also reviewed case report forms of patients treated as part of experimental studies of nimodipine and nicardipine for subarachnoid hemorrhage in greater Cincinnati hospitals during 1988. Two additional cases of subarachnoid hemorrhage that occurred during 1988 were identified. One patient's diagnosis had been coded improperly by medical record personnel during 1988. The second patient's chart was the only chart with a discharge diagnosis of subarachnoid hemorrhage that could not be located on the initial screening of medical records at the 20 hospitals.

Volume of subarachnoid hemorrhage was measured from the original CT films in the following manner. First, each CT image was placed on a light box, above which was fixed a video camera connected to a Joyce-Loebl Magiscan M2A Image Analysis computer. After obtaining an appropriate degree of clarity and brightness, an individual image was captured by the
camera, digitalized, and reproduced on the video monitor. Regions of subarachnoid hemorrhage were identified by a
neurologist, and the borders of the regions were then roughly approximated on the screen using image software.

The number of pixels constituting the subarachnoid hemorrhage was estimated using the records of the neurological examination; placement of an intraventricular drain; intubation; and cerebral angiography; hydrocephalus on CT; hyponatremia was estimated using the records of the neurological examination; made by the physician and nurses in the emergency room; date and time of stroke onset; the presence of signs; and grade 4a, Glasgow Coma Scale score of 13 to 14 with headache and/or nuchal rigidity but no focal signs; grade 3, localized clots of blood less than 1 mm thick; and grade 3, localized clots of blood in the occipital horns; and grade 2, blood occupying one full lateral ventricle with or without blood in the third or fourth ventricles; and grade 3, major intraventricular hemorrhage with blood packed into all ventricles and possible distension of the ventricular system.

Neurological function at presentation was measured by the World Federation of Neurological Surgeons Scale: grade 1, no headache or focal signs; grade 2, Glasgow Coma Scale score of 15 with headache and nuchal rigidity but no focal signs; grade 3, Glasgow Coma Scale score of 13 to 14 with headache and/or nuchal rigidity but no focal signs; grade 4a, Glasgow Coma Scale score of 13 to 14 with headache, nuchal rigidity, or focal signs; grade 4b, Glasgow Coma Scale score of 9 to 12 with headache, nuchal rigidity, or focal signs; and grade 5, Glasgow Coma Scale score of 8 or less and can have headache, nuchal rigidity, or focal signs. The Glasgow Coma Scale score, which is the main basis for the World Federation of Neurological Surgeons Scale, was often recorded on the life squad or emergency department records. For those cases in which a specific Glasgow Coma Scale score was not recorded in the medical record, the score was estimated using the records of the neurological examination made by the physician and nurses in the emergency department.

Other data abstracted from the medical record for this study included age, sex, race; admission blood pressure, pulse, and respiration; date and time of stroke onset; the presence of vasospasm and the location of aneurysms as determined by cerebral angiography; hydrocephalus on CT; hyponatremia (serum sodium less than 130 mEq/mL); operative clipping of ruptured aneurysm and time from symptom onset to operation; placement of an intraventricular drain; intubation; and antihypertensive therapy. For the 10 patients in whom the date but not the time of stroke onset could be accurately determined from the medical record, we assigned noon as the time of onset unless a patient arrived at the hospital before that time.

Rebleeding was defined as acute clinical deterioration that was accompanied by evidence of rebleeding in the subarachnoid space, ventricular system, or brain parenchyma by follow-up CT or autopsy. Increased seepage of blood into the ventricular system on subsequent CT scans was not included as recurrent bleeding. The diagnosis of clinical vasospasm was made using the following criteria: (1) classic symptoms of vasospasm that included onset 3 to 12 days after subarachnoid hemorrhage, worsening of headache, stiff neck, or low-grade fever, insidious onset of confusion, disorientation, or drowsiness, and new focal deficits that often fluctuated; (2) negative CT findings to exclude rebleeding and hydrocephalus; (3) no other identifiable cause of neurological worsening; and (4) confirmatory evidence on cerebral angiography when available.

Clinical outcome was graded from the medical records using a modified Oxford Handicap Scale as follows: 0, no symptoms; 1, minor symptoms that do not interfere with lifestyle; 2, minor handicap with symptoms that lead to some restriction in lifestyle but do not interfere with the patient’s capacity to look after himself; 3, moderate handicap with symptoms that significantly restrict lifestyle and prevent totally independent existence; 4, moderately severe handicap with symptoms that clearly prevent independent existence though not needing constant attention; 5, severe handicap with totally dependent patient requiring constant attention night and day; and 6, death.

Kaplan-Meier 30-day survival curves were calculated. Survival among men and women as well as whites and blacks was compared by log-rank test. Using 30-day mortality as the dependent variable, univariate logistic regression analysis was performed on the variables that were available at the initial medical evaluation as follows: age, race, sex, initial systolic blood pressure, volume of subarachnoid hemorrhage as measured by image analysis, volume of intraventricular hemorrhage, volume of parenchymal hemorrhage, and World Federation of Neurological Surgeons Scale score. Multivariate logistic regression analyses were then performed (including forward, backward, and stepwise modeling procedures) to determine the model that best predicted outcome at 30 days.

One multivariate analysis used death at 30 days as the dependent variable; another analysis used death or total dependency (Oxford Handicap Scale score of 5) at 30 days as the dependent variable. Comparisons between operated and nonoperated patients were made by $x^2$ and unpaired $t$ tests. Values of $P<.05$ (two-tailed) were considered significant. Data are presented as mean ± standard deviations except as indicated.

Results

There were 82 cases of spontaneous subarachnoid hemorrhage during 1988. Sixty-nine cases of subarachnoid hemorrhage were identified by CT, 11 by autopsy, and 2 by clinical evaluation and lumbar puncture. Of 71 hospitalized patients, 27 were admitted to the three tertiary-referral hospitals, and 44 patients were admitted to the remaining community hospitals.

Two causes of the 82 cases of subarachnoid hemorrhage were verifiable: ruptured aneurysm, as documented by angiography (34 patients) at autopsy (11 patients) or during the operative removal of an associated parenchymal hemorrhage (2 patients), and arteriovenous malformation (2 patients, both cases documented at autopsy). Of the remaining 33 hospitalized patients with subarachnoid hemorrhage, 11 had angio-
TABLE 1. Cause and Timing of Deaths After Onset of Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Cases</th>
<th>No. of Deaths</th>
<th>Cause and Day of Death (D-#)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial Bleed</td>
</tr>
<tr>
<td>Proven aneurysm</td>
<td>47</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>38</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td>Day 1-3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Day 4-7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Day 8 or more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No operation</td>
</tr>
<tr>
<td>Nonhospitalized/.autopsy cases</td>
<td>9</td>
<td>9</td>
<td>D-1,1,1,1,1,1,1,1</td>
</tr>
<tr>
<td>Probable aneurysm (no angiogram or autopsy)</td>
<td>20</td>
<td>18</td>
<td>D-1,1,1,1,1,1,1,1,2,4,5</td>
</tr>
<tr>
<td>No bleeding source</td>
<td>13</td>
<td>2</td>
<td>D-1,1</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>36</td>
<td>23</td>
</tr>
</tbody>
</table>

grams that showed no source of the subarachnoid hemorrhage. Two other patients had an autopsy that indicated no clear source of bleeding. The poor clinical condition of the rest precluded cerebral angiography. The median time from onset of subarachnoid hemorrhage to first medical evaluation was 50 minutes. The 2 cases of subarachnoid hemorrhage due to rupture of an arteriovenous malformation are excluded from the remaining analyses.

The mean age of the 80 patients with subarachnoid hemorrhage thought due to aneurysmal rupture was 54±13 years (31 men, 49 women; 61 white, 19 black). Of the 80 patients, 36 (45%) died within 30 days of onset. The 30-day mortality of patients admitted to one of the three referral hospitals (33%) was not significantly lower than the mortality of patients admitted to the remaining hospitals (41%). However, as noted in Methods, patients with subarachnoid hemorrhage that were referred from outside of the five-county region were excluded from analysis. These excluded patients would be expected to have a higher survival rate. The 67 patients with a documented or probable aneurysm had a 30-day mortality of 51% (Table 1). The 13 patients who had no evidence of a ruptured aneurysm by angiogram or autopsy had a 30-day mortality of 15% (Table 1).

Twenty-two deaths (61%) occurred within the first 2 days of onset, and 9 of 21 patients died before reaching the hospital (Figs 1 and 2, Table 1). One of the 22 very early deaths was caused by CT-documented rebleeding. Various causes of death in the remaining 14 patients who died after day 2 included rebleeding (7 patients), mass effect and herniation from a large intracerebral hematoma accompanying the subarachnoid hemorrhage (1), the initial subarachnoid hemorrhage (1, day 4), myocardial infarction (1), pneumonia (1), cardiac arrhythmia (1), hydrocephalus and clinical evidence of vasospasm (1), and brain damage secondary to cardiac arrest on day 1 and subsequent hydrocephalus, hyponatremia, and possible vasospasm (1).

Original CT films that were used to measure the volume of subarachnoid, intraventricular, and intraparenchymal hemorrhage were available for 59 of the 71 hospitalized patients. The mean volume of subarachnoid hemorrhage for the 59 patients was 21±22 cm³. Volume of subarachnoid hemorrhage was a powerful predictor of subsequent 30-day mortality in a univariate logistic regression analysis (P=.0001). Only 3 of the 29 patients with a volume of subarachnoid hemorrhage of 15 cm³ or less died before 30 days (Fig 3). Two of these 3 patients had documented rebleeding as the cause of death, and the third had 87 cm³ of intraventricular hemorrhage in addition to 6 cm³ of subarachnoid hemorrhage.

![Fig 1. Bar graph showing timing of deaths after onset of subarachnoid hemorrhage. Day of death (x axis) is in calendar days from stroke onset. Thus, a patient who had onset of subarachnoid hemorrhage on 3/4/88 and died on 3/5/88 was classified as dying on calendar day 1. Patients who died on calendar day 0 are included under calendar day 1 in the graph.](http://stroke.ahajournals.org/)

![Fig 2. Proportional graphic of causes of death among 80 patients with subarachnoid hemorrhage.](http://stroke.ahajournals.org/)
This patient with multiple aneurysms had rupture of a partially clipped ruptured aneurysm and died from rebleeding 27 days after the initial hemorrhage. Only 1 of the 8 patients with a volume of subarachnoid hemorrhage of 50 cm³ or more survived. Using Fisher's system of grading the amount of subarachnoid hemorrhage on the CT film, a similar relation between the amount of subarachnoid hemorrhage and mortality was seen. None of the 17 patients with grade 1 or grade 2 subarachnoid hemorrhage were dead at 30 days, whereas 24 (57%) of the 42 patients with a grade 3 hemorrhage died (P=.001, \( \chi^2 \) test). Intraventricular hemorrhage was present on the initial CT scan in 21 (36%) of 59 patients (mean volume for the 21 patients, 30±36 cm³) and was a significant predictor of 30-day mortality in the univariate analysis (P=.008). Classification of intraventricular hemorrhage by the Petruk Scale also significantly predicted 30-day mortality (P=.01, \( \chi^2 \) test). Intraparenchymal hemorrhage was present on the initial CT scan in 8 (14%) of the 59 patients (mean volume for the 8 patients, 27±26 cm³) but was not predictive of 30-day mortality.

The World Federation of Neurological Surgeons Scale score (P=.0001) and age (P=.005) were other significant predictors of 30-day mortality in the univariate analyses. Age (\( r=.48, P=.0001 \)) and the World Federation of Neurological Surgeons Scale score (\( r=.55, P=.0001 \)) were also significantly correlated with the volume of subarachnoid hemorrhage.

Only volume of subarachnoid hemorrhage (P=.01) and the World Federation of Neurological Surgeons Scale score (P=.006) remained significant independent predictors of 30-day mortality in the multivariate logistic regression analyses. In the analysis using death or total dependence at 30 days as the outcome variable, only age (P=.008) and the World Federation of Neurological Surgeons Scale score (P=.0001) were significant predictors of outcome.

Of the later events during hospitalization, rebleeding (\( \chi^2, P<.001 \)) and operative clipping of aneurysm (\( \chi^2, P<.001 \)) were significant predictors of 30-day outcome. All of the eight patients who had rebleeding died. Rebleeding occurred on day 1 (1), day 2 (2), day 5 (1), day 12 (1), day 16 (1), day 22 (1), and day 27 (1). Only 1 (3%) of the 31 patients who underwent operative clipping of a ruptured aneurysm died before 30 days. This patient with multiple aneurysms had rupture of a partially clipped ruptured aneurysm and died from rebleeding 27 days after the initial hemorrhage.
complex (posterior communicating artery, ophthalmic, and internal carotid artery) in 35%, the middle cerebral artery in 20%, the basilar artery in 7.5%, multiple aneurysms in 7.5%, and the posterior inferior cerebellar artery and vertebral arteries in 2.5%. No aneurysm location was associated with a significantly higher 30-day mortality, although the numbers in each category were small.

Other medical and operative therapies during hospitalization included an intraventricular drain in 17 patients (24%), nitroprusside for elevated blood pressure in 34 (48%), other drug treatment for hypertension in 60 (85%), and intubation in 44 (62%). Most patients who developed clinical vasospasm and had clipping of their ruptured aneurysm received hypervolemic therapy. One patient participated in a randomized study of nimodipine, 4 patients were participants in a randomized study of nicardipine, and 1 patient received nicardipine on a compassionate basis.

Of the 44 hospitalized patients who survived 30 days, 52% had mild or no handicap, 18% had moderate handicap, 16% had moderately severe handicap, and 14% were totally dependent at 30 days.

Discussion

Nearly two thirds of deaths following subarachnoid hemorrhage were due to the initial hemorrhage, and almost all of these deaths occurred during the first 2 days. Rebleeding accounted for 22% of 30-day mortality, whereas delayed arterial vasospasm contributed to only 6% of all deaths. These findings contrast sharply with the large International Cooperative Study on the Timing of Aneurysm Surgery1-2 in which delayed arterial vasospasm, rebleeding, and the initial hemorrhage each accounted for one fourth of all deaths. However, by design, the International Cooperative Study did not include patients with massive subarachnoid hemorrhage who died either before or soon after admission to the hospital or who had multiple bleeds before admission. The inherent selection bias in the International Cooperative study accounts for the proportional differences in the causes of mortality between our population-based study and treatment or tertiary-referral-based studies. This selection bias also explains the much lower 6-month mortality rate of 26% in the International Cooperative Study as compared with early mortality rates of 32% to 45% in the present and other population-based studies during the CT era.8,14-18

The rapidity of death for many patients with subarachnoid hemorrhage makes it very unlikely that any present or future short-term therapy will improve the grim outcome for these patients. Thus, the most effective means of preventing death due to subarachnoid hemorrhage are to limit the formation of aneurysms within the population and to safely identify and clip aneurysms likely to rupture before they do so. Modification of risk factors for aneurysmal subarachnoid hemorrhage, such as smoking and hypertension,19-21 may help limit formation and rupture of cerebral aneurysms. In addition, CT and magnetic resonance imaging have markedly enhanced the detection of unruptured intracranial aneurysms. The International Study of Unruptured Intracranial Aneurysms (ISUIA) is currently investigating whether clipping unruptured aneurysms of different sizes and locations can decrease the long-term morbidity and mortality caused by ruptured aneurysms (verbal communication, Dr David Wiebers, principal investigator, December 1993).

The level of responsiveness, as measured by the World Federation of Neurological Surgeons Scale score, and the volume of subarachnoid hemorrhage were two powerful independent predictors of 30-day mortality available at initial presentation. Previous population-based studies also have found that level of consciousness, as measured by the Hunt and Hess score or Glasgow Coma Scale score, is a strong predictor of early mortality.14-17,22 Volume of subarachnoid hemorrhage was not an independent predictor of 30-day mortality in these community studies except for the King’s County study.14 This study, in which only the CT reports and not the actual CT films were reviewed, found that the presence of subarachnoid hemorrhage on CT scanning was a significant predictor of outcome in a multivariate logistic regression analysis. To our knowledge, ours is the first population study to precisely measure the volume of subarachnoid, ventricular, and intraparenchymal hemorrhage in patients with subarachnoid hemorrhage. Our results suggest that there is a critical volume of subarachnoid hemorrhage below which survival is highly likely unless rebleeding occurs. None of the 29 patients with a volume of subarachnoid hemorrhage of less than 15 cm3 died except for 2 patients who had documented rebleeding and 1 patient who also had 87 cm3 of ventricular hemorrhage.

Older age was an independent predictor of poor outcome at 30 days as in other population-based outcome studies.15,16 Enlarged cerebrospinal fluid spaces due to brain atrophy, which is often seen in the elderly, is the likely explanation for the significant correlation between advancing age and the volume of subarachnoid hemorrhage in our study. However, volume of subarachnoid hemorrhage remained a significant independent predictor of 30-day mortality after adjusting for age.

Rebleeding was the second leading cause of death and, except for one case, occurred after the first day. Thus, it is the major preventable cause of death in patients hospitalized with subarachnoid hemorrhage. In addition, our 11% rate of rebleeding during the first 30 days, which is lower than rates in other studies,15,22-27 is likely an underestimate because of the strictness of our criteria. The importance of rebleeding as a cause of 30-day mortality adds to the rationale for early clipping of ruptured aneurysms. The Cooperative Aneurysm Study reported that early surgery does reduce the risk of rebleeding in patients with ruptured aneurysms.1,2 However, the overall outcome in patients with early and later clipping of aneurysms was not significantly different.1,2

In conclusion, studies that exclude patients who are moribund at admission grossly underestimate the importance of the initial hemorrhage28 and overestimate the importance of vasospasm1-2 as a cause of death and morbidity after subarachnoid hemorrhage in large populations. For the US population, approximately 15,000 cases of subarachnoid hemorrhage occur yearly.29 Our results suggest that approximately 6000 patients will die suddenly, from either the initial bleeding or rebleeding, but only 500 or so will benefit from the efforts of delayed cerebral vasospasm. The results provide further support for prevention as the most effective strategy for lowering mortality from subarachnoid hemorrhage.
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References

29. Broderick et al. Bleeding After Subarachnoid Hemorrhage 1347
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