SPECIAL ARTICLE

Simple Risk Predictions for Arteriovenous Malformation Hemorrhage

Douglas Kondziolka, M.D.,
Mark R. McLaughlin, M.D., John R.W. Kestle, M.D.

Department of Neurological Surgery (DK, MRMcL), Presbyterian University Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania, and Division of Neurosurgery (JRWK), Research Consulting Unit, British Columbia's Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

WE PRESENT A simple risk prediction formula for arteriovenous malformation hemorrhage. Natural history studies have shown an annual risk of hemorrhage of 2 to 4% for patients with brain arteriovenous malformations. Although decision analysis programs and biostatistical models are available to predict long-term risks of hemorrhage, we hypothesized that there was varying knowledge regarding the use of such programs within the general neurosurgical community. To obtain information on the current use of risk data, we performed a survey of neurosurgeons at national meetings in 1988 and 1994. Neurosurgeons were asked to define the risk for arteriovenous malformation hemorrhage in the young adult patient over a 20- to 30-year period, given a 3 or 4% annual risk of hemorrhage. A wide range of answers was obtained (1–100% risk), and many different methods of calculation were used. The use of the multiplicative law of probability formula requires only knowledge of patient age and annual hemorrhage risk. Risk of hemorrhage = 1 − (risk of no hemorrhage)$^{\text{expected years of remaining life}}$. The assumptions pertaining to this multiplicative formula include a constant yearly risk of hemorrhage and the independent behavior of all years of observation. We calculated the predictions of risk of hemorrhage across all age groups, as modified by published survival data. We think the use of this formula is justified by published natural history data across different ages and populations and that it is a simple and reasonable alternative to other methods of calculation. (Neurosurgery 37:851–855, 1995)

Key words: Arteriovenous malformation, Hemorrhage, Hemorrhage risk, Natural history

Recent studies have agreed that the annual risk for hemorrhage from a brain arteriovenous malformation (AVM) is ~2 to 4% (4, 6, 11, 12, 16, 17, 24, 25). This is useful information, but it needs to be used by surgeons to advise patients about the risk of bleeding over a number of years or over the remainder of their lives. One alternative is for the surgeon to inform the patient of a 2 to 4% risk per year. The interpretation of that figure is then left up to the patient. Most surgeons are asked for or think that they should provide the patient with a summary of the risk over a longer time period to give them a more representative idea of the natural history. Such information is often used as the basis for a decision to treat an AVM, along with expected treatment risks (29, 30). A decision analysis model has been published; it takes into account a number of risk factors and the patients' perception of the possible outcomes (9). This appears to be a good model, but it may be difficult to apply in day-to-day clinical situations. The two purposes of our study were as follows: 1) to survey practicing neurosurgeons and examine the ways in which they use published natural history data (usually stated as an annual risk of bleeding) to advise patients about their long-term (lifetime) prognosis; and 2) to propose a simple formula for calculating the risk of subsequent bleeding over a prolonged period of time, based on the multiplicative law of probability (5). This formula requires a number of assumptions and, as proposed, does not take into account some of the published risk factors for subsequent bleeding, but it is simple to use and may be a reasonable alternative for clinical use.

The problems with such an approach to risk estimation include population heterogeneity, a variable natural history, and the existence of patient sub-groups with different risks for initial and subsequent hemorrhage (e.g., pregnant women, patients with AVMs and aneurysms, patients with AVMs with venous outflow restriction) (3, 13, 19, 23, 26, 31, 33, 34). Although the estimated 2 to 4% yearly risk of hemorrhage has been substantiated in different countries and appears not to vary significantly through the course of follow-up, indicating

some degree of population homogeneity and predictable natural history, the interpretation of population data to specific patients must be approached with caution. It is not our purpose to use this formula and its assumptions to derive hemorrhage rates that represent mathematical fact but rather to derive rates that are reasonable, easy to use, and make sense with previously published clinical studies.

METHODS

The proposed method of calculation

If we assume that the annual risk of bleeding is 3% (0.03), then the chance of remaining free of hemorrhage for 1 year is $1 - 0.03 = 0.97$. The chance of remaining hemorrhage-free for 2 years is calculated by applying the multiplicative law of probability (5) as follows: $0.97 \times 0.97 = 0.94$. The chance of having no bleeds for y years = 0.97^y.

Patients will be at risk of subsequent bleeding for the rest of their lives. Based on the age of presentation, a patient's "expected years of remaining life" can be determined from life tables (1). Thus, the patients' cumulative chance of staying hemorrhage-free for life is equal to the following: $0.97^{\text{expected years of life}}$ or the risk of bleeding (at least once) = $1-0.97^{\text{expected years of remaining life}}$.

Consider this example. A 25-year-old man presents with a seizure and is found to have a small frontal AVM. His life expectancy is 77 years; he has 52 expected years of life remaining (1). Assuming a risk of hemorrhage of 3% per year, the risk is calculated as follows: risk = $1 - 0.97^{52} = 0.80$ or 80%. This calculation makes a number of assumptions as follows: 1) that the yearly risk of hemorrhage is constant (in an individual and a population); and 2) that the risk of hemorrhage in any given year is not influenced by (i.e., is independent of) events in other years.

Mortality from bleeding does not affect this calculation. We are calculating the probability of remaining free of bleeds over a period of time, and we are assuming that each year the probability of not bleeding is 0.97. Among the 0.03 patients who have bled, some (~5–20%) will die but this will not affect the proportion who are alive and hemorrhage-free at the end of the 1st year and remain at risk. The probability of living and not bleeding over x years then is 0.97^x and the probability of bleeding (whether or not death occurs from the bleed) = $1 - 0.97^x$.

A survey of neurosurgeons

We performed a survey of a convenience sample of neurosurgeons in 1988 at the meeting of the American Association of Neurological Surgeons in Toronto, Ontario, Canada. Each surgeon was stratified according to resident or attending status. Each individual was given an unlimited time period to answer one question. The following question was posed: "A neurologically intact 42-year-old woman presents with an arteriovenous malformation. She wishes to know what is the chance of having a hemorrhage in her lifetime, assuming a life expectancy of 30 more years and a 3% yearly risk of hemorrhage. Provide your answer and method of calculation."

In 1994, we administered a second random survey at the meeting of the American Association of Neurological Surgeons in San Diego, CA. The following question was posed: "A 25-year-old male presents with headache and is found to have a 2-cm arteriovenous malformation in the left frontal lobe. What is his risk for sustaining a hemorrhage over the next 20 years, assuming a 4% yearly risk for hemorrhage?" Again, information on resident or attending neurosurgeon status was requested.

RESULTS

The application of the formula

Risk estimates for patients from birth to age 85 years are calculated (assuming an annual risk of 3 or 4%) and presented in *Table 1*.

The surveys

In 1988, 16 individuals were surveyed. Eight were residents, and eight were attending neurosurgeons. One surgeon (6%) estimated the risk to be 60%. Three "guessed" at the risk and gave answers from 50 to 80%. Six respondents gave very high risks of 90 to 100%, and two answered 30%. Four gave no

TABLE 1. Lifetime Risk for Arteriovenous Malformation Hemorrhage

Age at Initial Presentation (yr)	Estimated Yr to Live[a]	Risk of Hemorrhage (%) (2%/yr)	Risk of Hemorrhage (%) (3%/yr)	Risk of Hemorrhage (%) (4%/yr)
0	76	79	90	96
15	62	71	85	92
25	52	65	80	88
35	43	58	73	83
45	34	50	65	75
55	25	40	53	64
65	18	31	42	52
75	11	20	29	36
85	6	11	17	22

[a] Estimates according to 1992 Preliminary Life Tables prepared by Metropolitan Life Insurance Company (1).

response. Using the multiplicative law of probability, the risk of hemorrhage is calculated to be 60%.

In the 1994 survey, 103 neurosurgeons were sampled. Twenty-eight of the total respondents were resident neurosurgeons, 72 were attending neurosurgeons, and 3 did not provide their level of training status. Eight individuals (8%) said they would use the multiplicative law of probability or gave a risk of 56%. They were equally distributed between residents and attending neurosurgeons. Twenty-four surgeons (23%) provided a "guess" between 50 and 79%. Fifty surgeons (49%) calculated an 80% total risk by multiplying a 4% per year risk by 20 years. Five surgeons (5%) calculated 4% as the total risk for hemorrhage. Fifteen (15%) surgeons provided a range of answers between 1 and 49% risk or greater than 80% risk, and one surgeon provided no answer. Using the multiplicative law of probability, the risk in this survey is calculated to be 56%. We considered a close answer to be within 25% of that calculated; this was provided by 18% of the surgeons.

DISCUSSION

The effort put forth by numerous institutions to understand the natural history of untreated AVMs has provided consistent information. The annual risk of hemorrhage from an untreated or incompletely obliterated AVM was found to be between 2 and 4% per year (4, 24). These natural history rates of subsequent bleeds are the basis for making management decisions. We were interested in the way surgeons used this information when talking to a hypothetical patient. In both surveys, we found that surgeons provided a wide range of responses and used a number of different methods to arrive at their response. Several authors have proposed detailed techniques for decision making based on published rates of AVM subsequent bleeds. Fisher (9) used Markov analysis to compare surgical and conservative options for a hypothetical patient weighing the factors of age, morbidity and mortality rates, risks of subsequent bleeds, and patient desires. Although such techniques may be valid, they are complex and may be difficult to use in the clinical setting. Iansek et al. (15) used an annual AVM hemorrhage risk of 1% and a surgical mortality risk of 8 to 10%, in addition to other predictors, to conclude that conservative management offered less attendant risk than surgical resection of AVMs, even over the long term. In that report, the authors used a hemorrhage rate lower than that reported in most studies and a surgical mortality rate higher than what could be achieved at most centers during the 1980s. Decision analysis techniques have also been applied to aneurysm data (8, 32).

Risk estimates for AVM hemorrhage are important because of the crucial role they play in guiding treatment. Successful complete microsurgical resection immediately eliminates the long-term risk of hemorrhage (2, 13, 14). For management options, such as stereotactic radiosurgery (21), endovascular embolization, or staged procedures, a latency interval before obliteration renders mandatory some consideration of the hemorrhage risk. If no treatment (conservative observation) is pursued, then the lifetime risks for AVM hemorrhage and potential mortality must be accepted and understood. We selected a 3% annual risk for *Table 1* as a conservative estimate between published data of 2 and 4%.

Because this formula demands that all predicted years act independently (a uniform natural history), the annual hemorrhage risk must be properly interpreted. For discussion, we will assume an annual risk of 3%. A common error is to multiply the 3% risk by the number of years of interest (the method used by many of the neurosurgeons in our survey). For example, a 10-year-old with 70 years of estimated life remaining does not have a 210% chance of lifetime hemorrhage. Luessenhop and Rosa (20) plotted patient age versus percentage probability of bleeding. Although their graph showed a 100% lifetime hemorrhage risk for patients younger than 40 years (which they admitted was incorrect), they plotted the risk for patients older than 40 years by directly multiplying 3% by the number of years remaining (i.e., a 50-year-old living to age 75 has a 75% chance of bleeding). The actual risk calculated by the multiplicative law of probability is 53% ($1 - 0.97^{25}$). This graph was later cited and reprinted in the natural history of AVMs review provided by Wilkins (36).

The application of the multiplicative law of probability is proposed as a simple and reasonable alternative method for AVM hemorrhage risk calculation. A number of assumptions are required in the application of this law and are discussed below.

Assumption 1: population homogeneity

Some degree of population homogeneity has been demonstrated by the results of studies performed in different nations. American (4, 11, 12), Japanese (16), Swedish (10), French (17), British (6), and Finnish (24) groups provided consistent data on the long-term risk of hemorrhage in untreated patients. Although individual patients within a population vary considerably in regard to age, AVM location, size, and hemodynamic pattern, the presence of associated aneurysms, and systemic physiological states (e.g., pregnancy, coagulopathy), the populations, as a whole, seem to be remarkably uniform. The assumption of overall population homogeneity seems reasonable.

Assumption 2: uniform natural history

To predict hemorrhage risk over the course of a lifetime, this formula assumes that each year of prediction is independent. For this to be true, the annual 3% hemorrhage risk must be applicable to young, middle-aged, and elderly patients. The traditionally held concept that the risk of an AVM hemorrhage is significantly lower in the elderly, does not hold up in reported studies. Although most series indicate a higher rate of clinical presentation at the 20- to 40-year age interval (27), the actual proportion of hemorrhagic to nonhemorrhagic AVM presentations remains fairly constant through the adult years. Parkinson and Bachers (25) studied 100 consecutive patients with brain AVMs and stratified the percentage of hemorrhagic presentations by decade; no significant differences were seen. In the study by Ondra et al. (24), with a mean follow-up of 24 years, the hemorrhage rates remained con-

stant through 5-year stratifications of the first 20 years of the study period (with some decline thereafter), regardless of patient age upon entrance into the study. Pregnancy (7) or hypertension might predispose patients to hemorrhage, but their significance in population risks is low. Robinson et al. (28) found no increase in risk of hemorrhage with increasing gestational age. As noted above, the hemodynamic factor of venous outflow restriction or the presence of proximal or intranidal aneurysms also might increase the risk for hemorrhage and must be identified and considered in individual patients. Although some reports note the occurrence of the spontaneous enlargement or regression of AVMs, this phenomenon appears to be infrequent enough as to not significantly contribute to a changing natural history (22, 35).

The risk of hemorrhage in the initial posthemorrhage year was reported by Graf et al. (12) to be 6%. Fults and Kelly (11) reported a 1st-year subsequent bleeding rate of 17.9% in their study, which declined to 2% per year after 10 years. However, in the largest study reported by Ondra et al. (24), the authors found that the 4% annual hemorrhage rate was constant over the 20-year follow-up interval and did not vary regardless of the manner of presentation (24). Thus, we found it reasonable not to include for the lifetime calculation risk a potentially short-term increased rate after a first bleed.

Few studies have addressed the hemorrhage risk of AVMs in children (age, <18 yr), which may be higher than in adults. Kondziolka et al. (18) reported 132 children with AVMs accrued over a 40-year period, with hemorrhage being responsible for 79% of clinical presentations. The higher proportion of patients with posterior fossa AVMs that present earlier in life with hemorrhage (these do not present with seizures) and potentially larger number of smaller lesions may explain this higher bleeding tendency. These reported observations do not mean, however, that AVMs in children *will* present with hemorrhage at a higher rate (e.g., >2–4%/yr) but that those that do, do so with hemorrhage. Because there is evidence that suggests some degree of natural history uniformity across different age groups, we thought this assumption was valid.

For AVMs, all current treatment alternatives mandate an understanding of the natural history of the risk of hemorrhage. Such an understanding is not only important for patient education and for comparison to our surgical results but also for the justification of the selection of a specific management strategy. The simplicity of this formula and its appropriateness for most patients with AVMs within the framework of addressed assumptions makes it a reasonable alternative for physicians who are managing these difficult problems.

Received, January 12, 1995.
Accepted, May 26, 1995.
Reprint requests: Douglas Kondziolka, M.D., M.Sc., F.R.C.S.(C), Associate Professor of Neurological Surgery and Radiation Oncology, Suite B-400, Presbyterian University Hospital, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213-2582.

REFERENCES

1. Arnold CD (ed): Record high life expectancy. **Stat Bull** 74:28–35, 1993.
2. Batjer HH, Devous MD, Siebert JB, Purdy PD, Bonte FJ: Intracranial arteriovenous malformations: Relationship between clinical factors and surgical complications. **Neurosurgery** 24:74–79, 1989.
3. Brown RD, Wiebers DO, Forbes GS: Unruptured intracranial aneurysms and arteriovenous malformations: Frequency of intracranial hemorrhage and relationship of lesions. **Neurosurgery** 73:859–863, 1990.
4. Brown RD, Wiebers DO, Forbes GS, O'Fallon WM, Piepgras DG, Marsh WR, Maciunas RJ: The natural history of unruptured intracranial arteriovenous malformations. **J Neurosurg** 68:352–357, 1988.
5. Colton T: Probability, in *Statistics in Medicine.* Boston, Little Brown, 1974, pp 66–71.
6. Crawford PM, West CR, Chadwich DW, Shae MDM: Arteriovenous malformations of the brain: Natural history in unoperated patients. **J Neurol Neurosurg Psychiatry** 49:1–10, 1986.
7. Dias MS, Sekhar LN: Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. **Neurosurgery** 27:855–866, 1990.
8. Dippel DWJ, Vermeulen M, Braakman R, Habbema JD: Transient ischemic attacks, carotid stenosis, and an incidental intracranial aneurysm: A decision analysis. **Neurosurgery** 34:449–458, 1994.
9. Fisher WS: Decision analysis: A tool of the future—An application to unruptured arteriovenous malformations. **Neurosurgery** 24 129–135, 1989.
10. Forster DMC, Steiner L, Hakanson S: Arteriovenous malformation of the brain: A long term clinical study. **J Neurosurg** 37:562–570, 1972.
11. Fults D, Kelly DL: Natural history of arteriovenous malformation of the brain: A clinical study. **Neurosurgery** 15:658–662, 1984.
12. Graf CJ, Perret GE, Torner JC: Bleeding from cerebral arteriovenous malformations as part of their natural history. **J Neurosurg** 58:331–337, 1983.
13. Heros RC, Tu YK: Unruptured arteriovenous malformations: A dilemma in surgical decision-making. **Clin Neurosurg** 33:187–236, 1985.
14. Heros RC, Korosue K, Diebold PM: Surgical excision of cerebral arteriovenous malformations: Late results. **Neurosurgery** 26:570–578, 1990.
15. Iansek R, Elstein AS, Balla JI: Application of decision analysis to management of cerebral arteriovenous malformations. **Lancet** 1:1132–1136, 1983.
16. Itoyama Y, Uemura S, Ushio Y, Kuratsu J, Nonaka N, Wada H, Sano Y, Fukumura A, Yoshida K, Yan T: Natural course of unoperated intracranial arteriovenous malformation: Study of 50 cases. **J Neurosurg** 71:805–809, 1989.
17. Jomin M, Lesoin F, Lozes J: Prognosis for arteriovenous malformations of the brain in adults based on 150 cases. **Surg Neuro** 23:362–366, 1985.
18. Kondziolka D, Humphreys RP, Hoffman HJ, Hendrick EB, Drake JM: Arteriovenous malformations of the brain in children: A forty-year experience. **Can J Neurol Sci** 19:40–45, 1992.
19. Kondziolka D, Nixon B, Lasjaunias P, Tucker W, TerBrugge KG, Spiegel S: Cerebral arteriovenous malformations and associated arterial aneurysms: Hemodynamic and therapeutic considerations. **Can J Neurol Sci** 15:130–134, 1988.
20. Luessenhop AJ, Rosa L: Cerebral arteriovenous malformations: Indications for and results of surgery and the role of intravascular techniques. **J Neurosurg** 60:14–22, 1984.

21. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette D, Jungreis CA, Horton JA, Maitz AH, Coffey RJ: Stereotactic radiosurgery for arteriovenous malformations of the brain. J **Neurosurg** 75: 512–524, 1991.
22. Minakawa T, Tanaka R, Koike T, Takeuchi S, Saki O: Angiographic follow-up study of cerebral arteriovenous malformations with reference to their enlargement and regression. **Neurosurgery** 24:68–74, 1989.
23. Miyasaka Y, Yada K, Ohwada T, Kitahara T, Kurata A, Irikura K: An analysis of the venous drainage system as a factor in hemorrhage from arteriovenous malformations. J **Neurosurg** 76:239–243, 1992.
24. Ondra SL, Troupp H, George ED, Schwab K: The natural history of symptomatic arteriovenous malformations of the brain: A 24-year follow-up assessment. J **Neurosurg** 73:387–391, 1990.
25. Parkinson D, Bachers G: Arteriovenous malformations: Summary of 100 consecutive supratentorial cases. J **Neurosurg** 53:285–299, 1980.
26. Pasqualin A, Barone G, Cioffi F, Rosta L, Scienza R, DaPian R: The relevance of anatomic and hemodynamic factors to a classification of cerebral arteriovenous malformations. **Neurosurgery** 28:370–379, 1991.
27. Perret G, Nishioka H: Arteriovenous malformations: An analysis of 545 cases of craniocerebral arteriovenous malformations and fistulae reported to the Cooperative Study. J **Neurosurg** 25:467–490, 1966.
28. Robinson JL, Hall CJ, Sedzimir CB: Subarachnoid hemorrhage in pregnancy. J **Neurosurg** 36:27–33, 1972.
29. Shi YQ, Chen XC: A proposed scheme for grading intracranial arteriovenous malformations. **J Neurosurg** 65:484–489, 1986.
30. Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. **J Neurosurg** 65:476–483, 1986.
31. Steinmeier R, Schramm J, Muller HG, Fahlbusch R: Evaluation of prognostic factors in cerebral arteriovenous malformations. **Neurosurgery** 24:193–200, 1989.
32. terBerg HWM, Dippel DWJ, Habbema JDF, Bijlsma JB, van Gijn J, Tulleken CAF, Willemse J: Treatment of intact familial intracranial aneurysms: A decision-analytical approach. **Neurosurgery** 23:329–334, 1988.
33. Viñuela F, Nombela L, Roach MR, Fox AJ, Pelz DM: Stenotic and occlusive disease of the venous drainage system of deep brain AVMs. J **Neurosurg** 63:180–184, 1985.
34. Waltimo O: The relationship of size, density and localization of intracranial arteriovenous malformations to the type of initial symptom. J **Neurol Sci** 19:13–19, 1973.
35. Waltimo O: The change in size of intracranial arteriovenous malformations. **J Neurol Sci** 19:21–27, 1973.
36. Wilkins RH: Natural history of intracranial vascular malformations: A review. **Neurosurgery** 16:421–430, 1985.

COMMENTS

This succinct article describes a practical and sound method of estimating the life-long risk of hemorrhage from an arteriovenous malformation (AVM) for a particular patient. It also allows the surgeon to make an estimate of the risk for a defined period of time. I think the patients generally have as much trouble as I have understanding the meaning of a "3 to 4% risk of hemorrhage every year." The frequent follow-up question from the patients is, "Does that mean that I will surely die from this AVM if I live for x number of years–an inevitable conclusion if the patient is 20 years old and the annual risk of hemorrhage is multiplied by the actuarially expected 50 or 55 years of survival. The authors have provided an intelligent answer to this question.

Roberto C. Heros
Miami, Florida

The authors provide us with an appropriate and useful analysis for predicting the risks of hemorrhage secondary to cerebral AVM. The statistical methods are sound and will benefit neurosurgeons who counsel patients regarding these lesions.

David G. Piepgras
Raymond G. Auger
Rochester, Minnesota

Neurosurgeons who deal with patients who have survived the rupture of an AVM are almost always asked to prognosticate with respect to future risk, because this is clearly a determining factor for a patient in accepting surgical excision or some other form of therapy that is not entirely risk-free. This approach (the use of the multiplicative law of probability formula requiring only patient age and annual hemorrhage risk) seems to be reasonable.

The authors recognize the inherent limitations of this method, which include but are not restricted to the following: 1) some patients are going to die from their recurrent hemorrhages; 2) pregnancy may predispose a patient to an increased risk of hemorrhage; 3) the risk of hemorrhage may be greater in the months immediately after the rupture of an AVM; 4) hemorrhage in pediatric patients may be associated with a higher rate of subsequent hemorrhage than in older patients; 5) patients with certain AVMs, such as those in the posterior fossa, have a higher mortality rate, and patients with certain AVMs, such as those with venous constriction or associated aneurysms, may be at higher risk of hemorrhage and death. All these limitations aside, it is still desirable to be able to show the patients this projection as an addition to the mere statement that their risk of hemorrhage is "2 to 4% per year."

I intend to have a copy of the table by Kondziolka et al. in my desk drawer, and I will use it not only in advising patients who have had AVM hemorrhage but also patients with multiple aneurysms who have had an aneurysmal rupture, because the bleeding rates are about the same. Are the differences in life expectancy between men and women not sufficiently great? Would it not have been scientifically useful to prepare separate lifetime risk tables for men and women?

Bryce K.A. Weir
Chicago, Illinois