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BACKGROUND AND PURPOSE: **Angioplasty and intra-arterial papaverine are promising treatments for severe symptomatic vasospasm after subarachnoid hemorrhage (SAH), but there is little information on the clinical factors that predict treatment outcome. We sought to determine variables for predicting functional outcome in this setting.**

METHODS: **We reviewed 81 consecutive patients with symptomatic cerebral vasospasm from aneurysmal SAH treated with percutaneous balloon angioplasty or selective intra-arterial papaverine infusion between 1990 and 2000 (105 procedures). Logistic regression analysis was used to assess the effect of various clinical and angiographic factors on outcome.**

RESULTS: **Mean patient age was 54 years (range, 29–88 years). Twenty-nine patients (36%) presented with poor-grade (World Federation of Neurologic Surgeons [WFNS] grade IV or V) SAH. Clinical deficits were global in 55 patients (70%), and angiographic vasospasm was diffuse in 53 (65%). Endovascular treatment consisted of transluminal angioplasty alone (18 procedures, 17%), intra-arterial papaverine infusion (65 procedures, 62%), or both (22 procedures, 21%). Unequivocal arterial dilatation was achieved in all but two patients, and major complications occurred in 2% of the procedures. Ten patients (12%) died in the hospital, and 36 (44%) recovered poorly. Permanent deficits attributable to cerebral vasospasm were present in 37 patients (52% of survivors). On multivariate logistic regression analysis, advanced age and poor WFNS grade at presentation were predictive of poor clinical outcome.**

CONCLUSION: **Advanced age and poor clinical status at the time of SAH onset are predictive of poor clinical outcome despite endovascular treatment with angioplasty or intra-arterial papaverine in patients with symptomatic vasospasm.**

As a result of early definitive repair of ruptured aneurysms, cerebral vasospasm has become a leading cause of death and disability after subarachnoid hemorrhage (SAH). When severe, hemodynamic augmentation may be insufficient to prevent or reverse ensuing ischemic damage. In patients with this condition, percutaneous balloon angioplasty and selective intra-arterial papaverine infusion are promising therapeutic alternatives (1–10). These interventions usually result in excellent angiographic results. However, clinical improvement does not always follow, and the impact of these treatments on outcome has been questioned (11, 12).

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Several protocols have been proposed to guide the use of these endovascular treatments. Although most accept their indication when patients develop ischemic deficits that fail to respond to optimal hemodynamic support, some groups advocate the preemptive use of balloon angioplasty in patients at high risk for cerebral vasospasm (13). Still, little is known about prognostic factors that are predictive of poor treatment results and that possibly justify earlier or more aggressive intervention.

We examined patients who required treatment with balloon angioplasty or intra-arterial papaverine infusion after failed hemodynamic augmentation. The purpose of our study was to determine variables for predicting functional outcome in patients with symptomatic cerebral vasospasm after aneurysmal SAH who undergo endovascular treatment.

Methods

We reviewed the clinical and radiologic information of all patients admitted to the Mayo Clinic, Rochester, MN, with acute aneurysmal SAH between 1990 and 2000. All patients had signed a written authorization allowing access to their

medical records for research purposes, and our Institutional Review Board approved the research protocol.

Patients were included in the study if a ruptured aneurysm had been documented by means of angiography; if admission to our institution had occurred within 7 days of SAH onset; and if symptomatic vasospasm had been confirmed angiographically and treated with angioplasty, selective intra-arterial papaverine infusion, or a combination of both. Patients with fusiform, traumatic, or mycotic aneurysms were excluded. We identified 84 consecutive patients who met these criteria from 415 patients treated in our institution for aneurysmal SAH during the study period. Three patients were excluded from further analysis because essential data could not be retrieved from their medical records.

Collected data included general demographic information, the date of SAH, the World Federation of Neurologic Surgeons (WFNS) grade at presentation (a poor grade was defined as a WFNS grade of IV or V), the location of the aneurysm, and the timing and type of endovascular intervention. Treatment of the aneurysm was either surgical clip placement or endovascular coil occlusion. Factors considered during the decision-making process included the aneurysmal dome-to-neck ratio, the presence of major or perforating branches off the aneurysm, and the surgical or endovascular accessibility.

Symptomatic vasospasm was defined as documented arterial vasospasm consistent with new neurologic deficits appearing between 4 and 14 days after the onset of SAH and not explained by other causes of neurologic deterioration (e.g., rebleeding, acute or worsening hydrocephalus, electrolyte disturbances, hypoxia, or seizures). Clinical deficits were classified as focal if the patient had new signs of neurologic impairment but remained alert or only drowsy. Global deficit was defined by the presence of stupor or coma (Glasgow Coma Scale sum score <10). Vasospasm was documented by means of conventional angiography in all cases. Severe angiographic vasospasm was considered present when there was narrowing of the arterial vessel lumen >50% of the normal caliber by visual inspection. Angiographic vasospasm was defined as focal if it was limited to either the anterior circulation on one side or the posterior circulation. Conversely, the vasospasm was considered diffuse if it was bilateral or involved vessels in both the anterior and the posterior circulations. We also tabulated the number of vessels involved in four categories: one vessel, two vessels, three vessels, or >three vessels. A neuroradiologist (D.A.N.) performed all angiographic assessments.

Medical management of vasospasm included use of colloids, use of crystalloids, and avoidance of antihypertensive drugs. Inotropic medications were used when deemed appropriate by the consulting neurointensivist. Endovascular intervention was considered after a patient's level of consciousness did not improve or when focal signs persisted. Angioplasty was always attempted when it was technically feasible. A single interventional neuroradiologist (D.A.N.) performed all endovascular procedures, and the decision for the use of papaverine or angioplasty was based on his clinical judgment.

The techniques used to perform intracranial balloon angioplasty or papaverine infusion continuously evolved during the 10 years of this retrospective review. In general, balloon angioplasty was used when vasospasm involved the intracranial carotid artery, the M-1 segment of the middle cerebral artery (MCA), the A-1 segment of the anterior cerebral artery (ACA), the intracranial vertebral artery, the basilar artery, or the P-1 segment of the posterior cerebral artery (PCA). Early in our experience, balloon angioplasty was performed by using investigational microcatheters with nondetachable silicone balloons specifically constructed for the treatment of vasospasm. More recently, balloon angioplasty was performed with commercially available over-the-wire angioplasty balloon microcatheters. Papaverine infusions were used when there was significant small vessel vasospasm not amenable to balloon angioplasty. Papaverine infusion solutions consisted of 250 mg of papaverine in 100 mL normal saline. When vasospasm was limited to the small distal vessels of the MCA, ACA, or PCA circulations, papaverine infusion was generally performed through a microcatheter placed in the M-1 segment of the MCA, the A-1 segment of the ACA or the P-2 segment of the PCA. Occasionally, papaverine infusions were performed through catheters placed in the cervical internal carotid artery when small vessels of both the ACA and MCA circulations were involved. The amount of papaverine infused depended on 1) whether the drug was infused globally into the internal carotid artery or more selectively into the proximal MCA, ACA, or PCA; 2) the number of circulations to be treated; and 3) the angiographic response to the infused papaverine.

TABLE 1: Distribution of WFNS clinical grades on admission

WFNS Grade	No. of Patients (n = 81)
I	29 (36)
II	16 (20)
III	7 (9)
IV	25 (31)
V	4 (5)

Note.—Data in parentheses are percentages.

Outcome was assessed by using the modified Rankin scale (mRS) at the time of last follow-up. A mRS score ≤2 was considered indicative of good functional outcome. We also recorded if the patient had permanent deficits attributable to cerebral vasospasm at the time of last evaluation. A neurologist trained in neurocritical care (A.A.R.) assessed the cause of residual deficits on the basis of the medical records.

We used descriptive statistics to study the distribution of demographic and clinical variables and the Fisher exact test to compare categorical variables. To assess the predictive value of various variables on treatment effect and clinical outcome, we performed logistic regression analysis by using statistical software (JMP; SAS Institute, Cary, NC). Unadjusted odds ratios were initially calculated for clinical and radiologic variables deemed likely to affect functional outcome. Multivariate logistic regression analysis was subsequently performed by using a model that included variables that had been predictive on univariate analyses. The results were expressed as odds ratios with 95% confidence intervals. Level of significance was established at $P < .05$.

Results

Eighty-one patients treated with angioplasty or intra-arterial papaverine for symptomatic cerebral vasospasm after aneurysmal SAH during the study period were included in the final analysis. Their mean age was 54 years (range, 29–88 years), and 70% were women. The distribution of WFNS grades on admission is shown in Table 1. Twenty-nine patients (36%) presented with poor-grade (WFNS grade IV-V) SAH. The ruptured aneurysm was located on the anterior circulation in 61 patients (75%) and in the posterior circulation in the remaining 20 patients (25%). Craniotomy and clip placement was performed in 66 patients (81%), and endovascular coil occlusion was performed in 15 (19%); poor-grade SAH was more common among patients treated with coil placement (47% vs. 33%), although the difference was not significant ($P = .4$) probably because of the low number of patients who received this type of treatment.

TABLE 2: Clinical outcomes

Outcome	No. of Patients (n = 81)
In-hospital death	10 (12)
Poor outcome*	36 (44)
Good outcome†	35 (43)

Note.—Data in parentheses are percentages.
*mRS score of 3–5.
†mRS score of ≤2.

TABLE 3: Clinical outcomes according to treatment

Treatment	Poor Outcomes*	Good Outcomes†
Papaverine	26 (56)	20 (43)
Angioplasty	8 (67)	4 (33)
Both	12 (52)	11 (48)

Note.—Data in parentheses are percentages.
*Death or mRS score of 3–5.
†mRS score of ≤2.

Only patients with symptomatic cerebral vasospasm were included in the analysis. Clinical deficits were global in 55 patients (70%), and angiographic vasospasm was diffuse in 53 (65%). Vasospasm involved one vessel in nine patients (11%), two vessels in 18 (22%), three vessels in 11 (14%), and >three vessels in the remaining 43 (53%). Vasospasm was treated with transluminal angioplasty alone in 12 cases (15%, 18 procedures [17%]), intra-arterial papaverine infusion alone in 46 cases (57%, 65 procedures [62%]), or both interventions in 23 cases (28%, 22 procedures [21%]).

Mean time to endovascular treatment was 8 days (range, 2–18 days). Fifty-eight patients (72%) received only one treatment, 22 patients (27%) had two treatments, and one patient (1%) was treated endovascularly on three occasions. Unequivocal arterial dilatation was achieved in all but two patients, although normalization of the diameter of the vessel lumen was not always achieved. Major periprocedural complications occurred in two of 103 interventions (complication rate of 2%): One patient had an internal carotid artery dissection, and another had a rupture of the first segment of the MCA.

Table 2 shows the clinical outcomes in our study population. Permanent deficits attributable to cerebral vasospasm were present in 37 patients (52% of survivors). Median follow-up was 3 months (range, 1 month to 8 years). Neither the type of clinical deficits (global vs. focal) nor the extent of angiographic vasospasm (diffuse vs. focal) was predictive of functional outcome (P = .6 for both comparisons). The type of endovascular treatment used was not correlated with the clinical outcome (Table 3). There was no correlation between year of treatment and functional outcome. We performed logistic regression analysis to identify variables of prognostic value. On univariate analysis, older age, poor WFNS grade at presentation (grade IV or V), and endovascular coil occlusion were significantly associated with worse clinical outcome (Table 4). On multivariate analysis, however, only older age and poor WFNS at presentation were predictive of poor clinical outcome (Table 5).

TABLE 4: Univariate analysis of predictors of poor outcome*

Variable	Odds Ratio	95% Confidence Interval	P Value
Age†	1.61	1.10–2.47	.02
Poor WFNS grade	3.66	1.38–10.66	.01
Anterior aneurysm	0.63	0.21–1.77	.4
Coiling	3.76	1.08–17	.05
Global deficit	2.39	0.93–6.31	.07
Diffuse vasospasm	0.78	0.30–1.97	.6
No. of affected vessels‡	1.29	0.38–4.36	.7
No. of endovascular treatments	1.17	0.2–7.7	.8

*mRS score of >2.
†Tabulated as a continuous variable in groups of 10-year intervals.
‡Tabulated as a continuous variable as one, two, three, and four or more vessels.

TABLE 5: Multivariate analysis of predictors of poor outcome*

Variable	Odds Ratio	95% Confidence Interval	P Value
Age†	1.66	1.09–2.67	.02
Poor WFNS grade	3.58	1.28–11	.02
Coiling	3.62	30.94–18	.08

*mRS score of >2.
†Tabulated as a continuous variable in groups of 10-year intervals.

Discussion

We reviewed our experience in 81 patients treated with intra-arterial papaverine infusion or percutaneous balloon angioplasty for symptomatic cerebral vasospasm and found that older age and poor clinical grade at presentation were predictive of worse clinical outcome. Coil embolization was associated with poor outcome in univariate but not in multivariable analysis, likely reflecting the worse clinical grade of patients treated with coiling during the study period. The treatments were generally safe and technically successful. Still, almost two-thirds of the patients died or remained disabled, and over one-half of the survivors had permanent deficits attributable to vasospasm.

Our results are comparable to those reported by Polin et al (11) but less encouraging than those published by Bejjani et al (3) and Rosenwasser et al (14). Nevertheless, 36% of the patients in our series had poor clinical grades at presentation. The proportion of patients with poor-grade SAH was lower in the series with better functional results (10% in the series by Rosenwasser et al and 13% in the series by Bejjani et al). This difference probably explains the discrepancies in clinical outcome between the studies.

Older age is associated with poorer functional recovery after SAH (15, 16). This observation is typically attributed to more severe effects of the initial

hemorrhage in the aging brain (16). In fact, the incidence of symptomatic vasospasm is greater in younger patients than in older patients (17–19), probably because of stronger vessel reactivity (19). However, the effects of vasospasm may be more deleterious in the aging brain. Our data show that endovascular treatment for symptomatic vasospasm becomes less effective in reducing functional disability as the age of the patient increases.

It has been argued that balloon angioplasty is superior to intra-arterial papaverine infusion for the permanent treatment of vasospasm (8, 20). This assertion has a solid theoretical background built on experimental and clinical evidence. The durable effects of angioplasty after stretching of the vessel wall are well documented (21, 22), whereas the vasodilatory action of papaverine is short lasting (23, 24). Comparing these two treatment modalities was not one of the primary objectives in this study. Moreover, since the treatment strategy depended on the interventional neuroradiologist's decision based on angiographic findings, the patients differed across the treatment groups. Patients treated with papaverine or a combination of both modalities were more likely than the others to have diffuse vasospasm or spasm involving small distal vessels. Hence, our finding that the type of endovascular treatment was not correlated with clinical outcome should be interpreted with caution.

Although most investigators agree that early interventional treatment of vasospasm may be beneficial, the optimal timing of endovascular modalities remains to be defined. While the best results may be obtained when treatment is provided within 2 hours (14) of the onset of symptoms, positive results may be seen with a therapeutic time window of up to 24 hours (3, 5). Meanwhile, prophylactic balloon angioplasty was proved feasible, and it led to a low incidence of symptomatic cerebral vasospasm, in a small group of patients with Fisher grade 3 SAH in a pilot study (13). In this report, we describe our experience in treating patients with symptomatic vasospasm refractory to hemodynamic augmentation therapy. By using a retrospective design, it was impossible to reliably reconstruct the chronologic evolution of the often-subtle and protracted symptoms due to vasospasm from the information recorded on the charts. Therefore, we were unable to assess the effect of treatment timing on clinical outcome in our population.

Arguably, patients with worse prognostic factors might benefit the most from early invasive therapy. We believe this study was the first to focus on identifying predictors of prognosis, specifically in patients undergoing endovascular treatment for severe symptomatic vasospasm. Our data showing that older patients with poor clinical grades at presentation did not improve despite endovascular treatment could be interpreted as a justification for earlier or even prophylactic intervention. On the other hand, it is possible that these patients may be poor candidates for endovascular treatment regardless of timing. Patients with a poor clinical grade may have already had permanent brain damage from the initial bleeding, and the condition in older patients may be more refractory to successful vessel dilation because of the presence of severe intracranial atherosclerosis (13) or impaired reactivity to papaverine (25).

Although angioplasty is usually a safe procedure in experienced hands, vessel rupture, branch occlusions, and episodes of rebleeding occasionally occur (5, 26, 27). Delayed complications from angioplasty have not been reported, and preliminary evidence suggests that vascular integrity and reactivity is preserved after the intervention (28). Our rate of complications from angioplasty was low despite having treated relatively old and severely ill patients.

Conclusion

Advanced age and poor clinical status at the time of SAH onset are predictive of poor clinical outcome despite endovascular treatment with angioplasty or intra-arterial papaverine in patients with symptomatic vasospasm. Patients with these poor prognostic factors could benefit from earlier or even prophylactic endovascular intervention. This hypothesis should be evaluated in future studies.

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