Is Asymptomatic Vasospasm Associated With Poor Outcome in Subarachnoid Hemorrhage?

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Abstract

Background: Vasospasm occurs in up to 70% of aneurysmal subarachnoid hemorrhage (aSAH), but only half becomes symptomatic. It is unclear whether asymptomatic vasospasm (AV) detected by noninvasive testing affects outcome. Prophylactic hemodilutional, hypertensive, and hypervolemic (HHH) therapy is widely used but the benefit remains unproven. We aim to determine whether AV increases the risk of poor outcome and whether HHH is safe. **Methods:** A total of 175 consecutive patients with aSAH without clinical vasospasm were included. Patients with sonographic (transcranial doppler) or radiologic (computed tomography [CT] Angiography) vasospasm were assigned to AV group, while those without were assigned to no vasospasm (NV) group. Logistic regression was used to determine the association between AV and HHH on poor outcome, defined as modified Rankin scale (mRS) >3 at discharge or 3 to 6 months' follow-up. **Results:** In all, 106 patients had NV and 25 received HHH. A total of 69 patients had AV and 54 received HHH. Asymptomatic vasospasm compared to NV was not associated with poor outcome (odds ratio [OR] 2.6, 95% confidence interval [CI]: 0.75-8.9; $P = .1$). Hemodilutional, hypertensive, and hypervolemic use in patients with AV did not improve the outcome (OR 0.16, 95%CI: 0.009-2.84; $P = .2$). In patients with NV, HHH use showed trend toward poor outcome after multivariable adjustment (OR 12.6, 95%CI: 1.08-146.5 $P = .04$). **Conclusion:** Asymptomatic vasospasm does not appear to be associated with poor outcome in aSAH. Hemodilutional, hypertensive, and hypervolemic therapy in AV was not associated with improved outcome and may be harmful to patients who do not have vasospasm. Further research is needed to validate this finding.

Keywords

subarachnoid hemorrhage, cerebrovascular disorders, vasospasm, intracranial, neurocritical care, clinical specialty

Introduction

Cerebral vasospasm remains the most important preventable cause of secondary brain injury after aneurysmal subarachnoid hemorrhage (aSAH) and occurs in up to 70% of patients. However, only about half of the patients with radiologic vasospasm becomes symptomatic.¹ There is general consensus on the treatment of symptomatic vasospasm which include both hemodynamic and endovascular manipulations.² However, management of cerebral vasospasm without clinical manifestation (AV) is controversial³ partly because its impact on patient outcome is unclear. An magnetic resonance imaging (MRI) study detected new infarction in 23% of patients with asymptomatic vasospasm (AV), but its impact on patients' global functional outcome was not studied.⁴ In a more recent report, silent infarction was seen in 20% of patients with AV, but the authors included comatose patients in the analysis thereby confounding the association of silent

infarction with poor outcome.⁵ On the other hand, patients who do not develop clinical or radiologic evidence of vasospasm are frequently given prophylactic hemodilutional, hypertensive, and hypervolemic (HHH) therapy to prevent the development of vasospasm despite absence of clear benefit.⁶ The purpose of our study is to determine whether the development of AV is an independent predictor of functional outcome in patients with aSAH. In addition, we want to

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determine the effect of prophylactic HHH therapy in this subgroup of patients.

Methods

Study Design

This is a retrospective case series of consecutive patients admitted to a tertiary care university hospital. The study was designed and conducted following the STROBE guidelines.⁷ The study proposal was reviewed and approved by the local institutional review board and informed consent was waived.

Study Population

Patients were included if they were older than 17 years, alive after 72 hours of hospitalization, and underwent aneurysm repair within 72 hours of symptom onset. Patients who had symptomatic vasospasm (defined as development of new focal neurologic abnormality and/or deterioration in the level of consciousness attributed to cerebral ischemia after excluding seizure, hydrocephalus, infection, metabolic abnormality, or drug effects) or nonaneurysmal cause of SAH were excluded from the study. For the purpose of the study, persistently comatose patients (including patients who could not be evaluated clinically because of need for medical neuromuscular paralysis and deep sedation) who developed radiologic or sonographic evidence of cerebral vasospasm were considered to have symptomatic vasospasm and were also excluded.

Patient Management

All patients were admitted to the neurocritical care unit and treated according to the published guidelines.^{8,9} Clinical severity was determined using the Hunt and Hess grade.¹⁰ The amount of subarachnoid blood was qualified using the Fisher group classification.¹¹ All patients with intracerebral aneurysm on computed tomography (CT) or conventional angiogram were treated with either surgical clipping or endovascular coiling within 24 hours of admission based on collective decision among neurosurgery, neurointerventional, and neurocritical care team. Patients with clinical or radiographic evidence of hydrocephalus received external ventricular drains (EVDs) prior to or during aneurysm repair. All patients were treated with a 21-day course of oral nimodipine and antiepileptic prophylaxis using phenytoin or levetiracetam. Transcranial Doppler ultrasonography (TCD) was done daily on all patients and vasospasm was defined as TCD peak systolic velocity >200 cm/s or TCD mean flow velocity >120 cm/s in any of the major intracranial vessels. Confirmatory CT angiography or conventional angiography was done in patients with symptoms or TCD velocity elevation and vasospasm was defined as diameter narrowing $>25\%$ from baseline or $>50\%$ from normal if no baseline study. For the purpose of the study, AV was defined as presence of TCD, CT angiography, or conventional angiography evidence of

vasospasm without associated clinical symptoms. All patients with clinical and most patients with TCD or angiographic vasospasm were treated with HHH (hemodynamic augmentation to systolic blood pressure >160 mm Hg, hypervolemia to central venous pressure = 8-12 cm H₂O, and hemodilution to hemoglobin = 10-12 g/dL) until the resolution of clinical or angiographic vasospasm. The decision to institute HHH in asymptomatic patients with or without imaging evidence of vasospasm was left at the discretion of the neurocritical care service. Medically refractory vasospasms or patients with clinically significant symptoms were treated with balloon angioplasty or intra-arterial infusion of vasodilators (papaverine, verapamil, nicardipine, and/or milrinone).

Data Collection

Electronic medical records and paper charts of included patients were reviewed. Demographic and clinical characteristics were recorded including age, sex, Hunt and Hess grade, Fisher group, aneurysm location and size, number of aneurysms, medical history of hypertension, diabetes, heart disease and stroke, presenting symptoms of sentinel headache, seizure, loss of consciousness and prehospital worsening, admission CT evidence of infarction, intraparenchymal bleed, hydrocephalus, cerebral edema, intraventricular hemorrhage and midline shift, and admission glucose level. In addition, patient management data were collected including emergent EVD placement, method of aneurysm repair, time from symptom onset to aneurysm repair, blood transfusion, sugar control, and HHH therapy.

Outcome Measures

Dichotomized global functional outcome using modified Rankin scale (mRS) was used. Good outcome was defined as an mRS ≤ 3 , and poor outcome was defined as an mRS > 3 . We choose modified Rankin score of 4 and higher to indicate poor outcome because this dichotomized patient who are relatively dependent for care and unable to ambulate (mRS score above 3) from patients who can ambulate independently and required minimal assistance (mRS score of 0-3). Outcome assessment was obtained from outpatient records at 3 to 6 months follow-up. In patients who did not have a follow-up record, the outcome was based on physical therapy notes recorded at the time of discharge or physician discharge examination.

Statistical Analysis

All data were analyzed with SAS for Windows software version 9.1.3 (SAS Institute Inc., Cary, North Carolina). Categorical data were analyzed using Fisher exact tests or chi-square tests as appropriate. Continuous data with normal distributions were reported as mean $\pm$ standard deviation and analyzed with Student *t* tests, while those with nonnormal distributions

were reported as median (interquartile range) and analyzed with Wilcoxon 2-sample tests. The crude effect of AV on outcome was determined using a chi-square analysis. Multivariable adjusted logistic regression models were then used to evaluate the independent relationship of AV on poor outcome. For all regression models, adjustment was done by age, sex, Hunt and Hess clinical grade, and Fisher group. A priori variables that were associated with poor outcome in prior studies such as interval from symptom onset to aneurysm repair, method of aneurysm repair, history of hypertension, and admission glucose level, in addition to variables showing a $P < .10$ on the respective univariate analyses were individually added in the regression model to detect changes in parameter estimate. A change of greater than 10% in the parameter estimate of the AV group was considered criterion for including the variable of interest in the final model. To correct for the effect of temporal trend, an interrupted time series analysis using year of admission as a linear function was included in the regression model. Corrections for multiple comparisons were done using the Bonferroni method and a value of $P < .025$ was considered statistically significant. Based on our sample size, our study had a power of 70% to detect a 25% absolute difference in good versus bad outcome with a 2-tailed α set at .025.

Results

A total of 175 patients (68% female and 32% male) with aSAH who did not develop clinical vasospasm were evaluated. The mean age was 56 ± 14 years (range 18-91 years). About 18% of patients had Hunt and Hess grade >3 on admission and 25% had Hunt and Hess grade <2 . Based on admission CT, 85% of patients belong to Fisher group 3 or 4. In all, 106 patients did not have any clinical or radiosonographic evidence of cerebral vasospasm and were classified in the no vasospasm (NV) group. Sixty nine (69) patients had radiosonographic evidence of vasospasm based on TCD or CT/conventional angiography without clinical manifestation and were classified in the AV group. The clinical and demographic characteristics of both groups were presented in Table 1. Patients in the NV group were older and had more history of hypertension, prehospital worsening, and loss of consciousness. Patients in the AV group had lower admission blood glucose, less evidence of cerebral edema, and midline shift on admission CT. Surgical repair was more common than endovascular coiling in the AV group, but other aspects of patient treatment were similar between the groups (see Table 2).

Asymptomatic Vasospasm and Outcome

The occurrence of AV was not found to be an independent risk factor for poor outcome (adjusted odds ratio 2.5, 95% confidence interval [CI]: 0.7-8.9; $P = .13$). Exclusion of poor Hunt and Hess grade patients in NV group (adjusted OR 3.2, 95%CI 0.8-13.4; $P = .10$), or changing the poor outcome definition to

mRS 3 to 6 (adjusted OR 1.8, 95%CI: 0.6-5.5; $P = .27$) did not change the result during sensitivity analysis. On the other hand, ICU length of stay and total length of stay among patients who developed AV were significantly longer and was not accounted for by development of new organ failure or systemic complications (see Table 3).

Triple HHH Therapy and Outcome

Among patients without clinical or radiosonographic evidence of cerebral vasospasm, 25 patients (24%) were treated prophylactically with HHH therapy. Of the patients who developed AV, 54 patients (74%) received HHH therapy. Prophylactic triple H therapy was not found to be associated with poor outcome (adjusted OR 0.77, 95%CI: 0.25-2.4; $P = .64$) but showed trend toward harm in patients without radiosonographic evidence of vasospasm (adjusted OR 12.6, 95%CI: 1.08-146.5; $P = .043$; see Table 4).

Discussion

In this study, we tried to determine the independent effect of development of AV as diagnosed by TCD and/or CT/conventional angiography. Using a global measure such as the mRS several months after hospitalization to evaluate functional outcome, we were unable to find association between the development of AV during hospitalization and high mRS score. Although we did not observe an increase in systemic complications or development of new organ failure in patients who developed AV, there was a statistically significant increase in both the ICU and total hospital length of stay compared to patients who did not have vasospasm. This is likely due to increased use of HHH therapy and ICU/hemodynamic monitoring.

Patients who develop AV may be at increased risk of delayed ischemic neurologic deficit and infarction. Absence of symptoms may be related to the noneloquent area affected by vessel narrowing and may not necessarily be benign. In fact, new infarction has been found in 21% to 23% of patients with AV,^{4,5} but its effect on functional outcome remains unclear since comatose patients were not excluded in the analysis. We have excluded comatose patients in our analysis to reduce the confounding effect of severity of illness on outcome of patients. Identifying patients at risk of infarction may be an important tool in selecting patients who may benefit from more individualized treatment strategies.

The management of patients with aSAH who develop radiosonographic evidence of cerebral vasospasm but without symptoms is contentious. The controversy is partly due to the unclear association of AV and outcome.¹² In addition, HHH which is the most common prophylactic therapy associated with the management of AV seems to be ineffective in improving cerebral blood flow and preventing the development of delayed ischemic deficit¹³ and may be harmful and costly.¹⁴ In our study, we have shown that prophylactic HHH

Table 1. Patient Demographic Characteristics

Characteristics	No Vasospasm N = 106 Mean $\pm$ SD, n (%), Median (25%, 75%)	Asymptomatic Vasospasm, N = 69 Mean $\pm$ SD, n (%), Median (25%, 75%)	P Value
Male sex ^a	35 (33.0)	21 (30.4)	.74
Age (year) ^a	59.9 $\pm$ 14.7	50.8 $\pm$ 12.2	<.01
Aneurysm characteristics			
Anterior aneurysm location	66 (62.3)	42 (60.9)	.87
Number of aneurysm	1 (1, 2)	1 (1, 2)	1.0
Aneurysm size (mm)	7 (5, 10)	6 (5, 8)	1.0
Patient presentation			
Sentinel headache	10 (9.4)	9 (13.0)	.47
Seizure at onset	5 (4.7)	2 (2.9)	.70
Loss of consciousness ^a	48 (45.3)	19 (27.5)	.03
Prehospital worsening ^a	20 (18.9)	3 (4.4)	.01
Hx of hypertension ^a	52 (50)	22 (32.4)	.03
Hx of diabetes ^a	11 (10.6)	2 (2.9)	.08
Hx of stroke	11 (10.6)	3 (4.5)	.25
Hx of CAD	12 (11.5)	6 (8.8)	.62
Hx of tobacco use	48 (60.0)	38 (65.5)	.59
Hunt and Hess grade ^a			
Hunt and Hess 1	22 (20.8)	21 (30.4)	
Hunt and Hess 2	18 (17.0)	14 (20.3)	
Hunt and Hess 3	33 (31.1)	34 (49.3)	
Hunt and Hess 4	25 (23.6)	0	
Hunt and Hess 5	8 (7.6)	0	
Poor Hunt and Hess grade ^b	33 (31.1)	0	<.01
Admission laboratory/imaging			
CT sign of edema ^a	25 (23.6)	8 (11.6)	.05
CT sign of infarction	4 (3.8)	0	.15
CT sign of ICH	21 (19.8)	9 (13.0)	.31
CT sign of IVH	77 (72.6)	51 (73.9)	1.00
CT sign of hydrocephalus	78 (73.5)	54 (78.2)	.59
CT sign of MLS ^a	17 (16.0)	3 (4.4)	.03
Fisher group ^a			
Fisher group 1	1 (0.9)	0	
Fisher group 2	10 (9.4)	11 (15.9)	
Fisher group 3	88 (83.0)	56 (81.2)	
Fisher group 4	7 (6.6)	2 (2.9)	
Poor Fisher group	88 (83.0)	56 (81.2)	.84
Admission glucose ^a	167.3 $\pm$ 63.5	150 $\pm$ 44.2	.05

Abbreviations: SD, standard deviation; CT, computed tomography; CAD, coronary artery disease; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; Hx, history of; MLS, midline shift.

^a Included in multivariate logistic regression analysis.

^b Poor Hunt and Hess grade = Hunt and Hess 4 and 5.

Table 2. Patient Management by Group

Patient Management	No Vasospasm, n = 106, N (%)	Asymptomatic Vasospasm, N = 69, n (%)	P Value
Time in days from symptom onset to repair of aneurysm, median (25%, 75%)	1 (1,2)	1 (1,2)	.65
Number of patients who underwent surgical aneurysm repair ^a	78 (73.6)	61 (88.4)	.02
Need for emergent EVD	74 (69.8)	45 (65.2)	.62
Blood transfusion	58 (54.7)	41 (59.4)	.64
Postop steroid use	66 (62.2)	46 (66.7)	.62
Number of patients with adequate glucose control	34 (32.0)	27 (39.0)	.42
No follow-up	22 (24.4)	14 (22.2)	.84

Abbreviation: EVD, external ventricular drain.

^a Included in multivariate logistic regression analysis.

Table 3. Patient Outcome in Relation to Development of Asymptomatic Vasospasm

	No Vasospasm, N = 106	Asymptomatic Vasospasm, N = 69	
Poor outcome = mRS 4, 5, 6, N (%)	35 (33.0%)	12 (17.4%)	^a OR = 2.5; 95% CI 0.7-8.9; P = .13
Poor outcome = mRS 3, 4, 5, 6, N (%)	42 (39.6%)	14 (20.3%)	^a OR = 1.8; 95% CI 0.6-5.5; P = .27
Poor outcome (excluding patients with poor Hunt and Hess grade), n/N (%)	10/73 (13.7%)	12/69 (17.4%)	^a OR = 3.2; 95% CI 0.8-13.4; P = .10
Poor Outcome (excluding patients who died in the hospital and/or no outpatient follow-up data), n/N (%)	10/68 (14.7%)	5/48 (10.4%)	^a OR = 3.1, 95% CI: 0.4-21.5; P = .24
Mortality, N (%)	18 (17%)	8 (12%)	P = .38
Number of new organ failure, ^b median (25%, 75%)	2 (0, 4)	2 (1, 4)	P = .59
ICU length of stay, median (25%, 75%)	10 (7, 13)	13 (11, 16)	P < .01
Total hospital length of stay, median (25%, 75%)	15 (10, 20)	17 (14, 23)	P < .01

Abbreviations: OE, odds ratio; CI, confidence interval; ICU, intensive care unit; mRS, modified Rankin scale.

^a Adjusted odds ratio from logistic regression analysis.

^b New organ failure was defined as development of any one of the following: cardiac dysfunction was defined as new evidence of congestive heart failure (documented by abnormal wall motion contractility or hypokinesia and ejection fraction <40% with clinical or radiographic evidence of pulmonary congestion) and/or development of acute myocardial infarction (documented by new electrocardiogram [ECG] evidence of myocardial injury associated with troponin elevation above 0.1 ng/mL and/or new segmental hypokinesia on echocardiography); respiratory failure was defined as hypoxemia requiring ventilatory support or failure to extubate within 24 hours postoperatively; renal failure was defined as >50% elevation in baseline creatinine or azotemia requiring renal replacement therapy; hepatic failure was defined as new hepatic enzyme elevation more than 3× the normal laboratory range.

Table 4. Relationship Between the Use of HHH and Proportion of Poor Outcome at 3 to 6 Months in Patients With and Without Asymptomatic Vasospasm

No Vasospasm, N = 106			Asymptomatic Vasospasm, N = 69		
HHH Therapy			HHH Therapy		
	Yes = 25	No = 81	^a OR = 12.6		
Proportion of	11 (44%)	24 (30%)	95% CI 1.1-146.5, P = .04	Proportion of	Yes = 54
poor outcome				poor outcome	No = 15
					^a OR = 0.16
					95% CI 0.1-2.8, P = .21

Abbreviations: HHH, Hemodilutional, Hypertensive, Hypervolemic therapy; OR, Odds Ratio; CI, Confidence Interval.

^a Odds ratio from logistic regression analysis adjusted for sex, age, coiling vs clipping, Hunt and Hess grade, Fisher group, year of admission, loss of consciousness on presentation, and history of hypertension (see Statistical Analysis for details).

therapy does not affect the outcome of patients. More importantly, we have determined that the use of prophylactic HHH in patients without evidence of vasospasm is associated with poor outcome and supports the findings of other authors of the danger of HHH if used in unselected patients.^{6,14,15} The hemodynamic and cerebral effect of different components of HHH therapy has been evaluated in recent years and may in part explain the variability in results with the clinical use of HHH in patients with SAH. Induced hypertension has been shown to have the greatest impact on improving regional cerebral blood flow,^{16,17} with no additional benefit from additional hypervolemic hemodilution.^{13,16,18}

Our study has a number of limitations. First, a significant number of patients had no available follow-up assessment (23%) and discharge assessments by either physical therapist or discharging physician were used to determine functional outcome. However, both of our comparison groups had equal proportion of patients without follow-up data. In addition,

among patients with follow-up data, majority of patients improved by 1 or 2 points in the functional scale and less than 3% of patients deteriorated, suggesting that the discharge evaluation maybe considered a conservative estimate of the eventual functional status of the patients. More importantly, limiting the analysis to only patients with outpatient records did not significantly alter the results (see Table 3). Second, we only used a dichotomized global functional scale for the outcome measure. A more comprehensive neuropsychologic and cognitive testing may be appropriate to determine the overall impact of AV as recent studies have shown significant psychosocial and cognitive difficulty among survivors of SAH despite functional independence.^{19,20} Third, the diagnosis of vasospasm in our cohort relied heavily on TCD with or without CT/conventional angiography. Patients with normal TCD velocities were not subjected to other vessel imaging and might have increased the misclassification of patients. However, TCD has very high specificity²¹ and has been shown

to be a good screening method for detecting vasospasm. Fourth, only clinical examination and observation were used to determine presence of absence of symptoms in patients with radiosonographic vasospasm. As patients with vasospasm in noneloquent cortical areas may remain asymptomatic despite significant perfusion abnormality, use of diagnostic testing to determine regional cerebral blood flow, cerebral metabolism, and oxygenation may help in risk stratifying patient who may benefit from therapy despite absence of symptoms. Fifth, because of the retrospective nature of our study, we were unable to quantify the hypervolemic therapy received by each patient. In addition, variable hemodynamic parameter goals were used without standardized duration, different vasopressor types and quantities were used, and hemodilutional end points were not well defined. Also, the type and duration of antiepileptic medications used were not documented for each patient. Sixth, the documentation of new cerebral infarction is limited by the absence of MRI studies in most patients. Seventh, the seemingly high percentage of poor outcome in the asymptomatic group is likely a reflection of the study design as poor Hunt and Hess grade patients were purposefully excluded in the analysis of patients who developed sonoradiologic vasospasm. Lastly, we consider our results preliminary and hypothesis generating, requiring further study for validation due to the inherently low power of our results (power analysis estimate of less than 63%) despite our stricter criteria for significance.

Conclusion

Asymptomatic vasospasm does not appear to be associated with poor functional outcome measured by mRS in aSAH. Prophylactic HHH therapy was not associated with better outcome in patients with AV and may be harmful to patients who do not have radiosonographic evidence of vasospasm. Further research is needed to validate this finding.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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