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Hematologic Predictors of Endovascular Retreatment for Recurrent Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Weston Gordon[1*], Brenton Massey[1], Adam Ranellone[2], Sanjeev Keshary[1], Kartavya Sharma[1] and Michael Abraham[1]

[1]The University of Kansas Health System, Kansas, USA

[2]Kansas University of Medicine and Biosciences, Kansas City, USA

***Corresponding author:** Weston Gordon, The University of Kansas Health System, Kansas, USA, Tel: +636- 675-0141; E-mail: wgordon@kumc.edu

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Abstract

Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (aSAH) is associated with a high degree of morbidity and mortality and is well established as a predictor of poor functional outcome, Endovascular interventions involving intra-arterial infusion of vasoactive agents or balloon angioplasty are frequently employed in the management of symptomatic cerebral vasospasm following aSAH. Many of these patients suffer from recurrent vasospasm and often require multiple endovascular treatments; however, there have been very few investigations to assess predictors of retreatment and they have produced inconsistent results.

Keywords: Subarachnoid hemorrhage; Aneurysm; Cerebral vasospasm; Endovascular procedure

Introduction

The mechanism of vasospasm following aSAH is incompletely understood, but the complicated cascade of events has been shown to involve pro-inflammatory pathways that occur in concert with micro-thromboses. Putative mechanisms include an increase in nitric oxide (NO) scavengers, proliferation of smooth muscle cells, and the up-regulation of adhesion and chemotactic factors including IL-1, IL-6, IL-8, TNF-α, macrophages, and MMPs. It is not surprising that increased white blood cell count, likely a result of increased inflammatory and chemokine activity, has been shown to correlate with occurrence of symptomatic vasospasm and mortality in patients with aSAH. Within the subset of patients with vasospasm, it is conceivable that some of these routinely obtained hematologic markers could serve as potential predictors of recurrent or refractory vasospasm.

The aim of this study was to investigate the association of hematologic parameters with recurrent clinical vasospasm (defined as acute alteration of mental status, new focal neurological deficits, or both) requiring repeat endovascular treatment.

Methods

Patient selection

The institutional review board (IRB) at The University of Kansas School of Medicine approved the study CR00005809. The IRB waived the need for written informed consent due to the retrospective design of the study. The database was comprised of 387 SAH patients from 2009-2016 at The University of Kansas Medical Center. We identified 279 consecutive aSAH patients. Patients were included in the study if they had aSAH and subsequently developed cerebral vasospasm requiring endovascular treatment. Inclusion criteria were: age > 18 years; diagnosis of SAH confirmed by non-contrast head CT; evidence of aneurysm on CT-angiography (CTA) or cerebral angiogram; diagnosis of cerebral vasospasm by CT-angiogram or catheter angiography; and endovascular treatment of vasospasm using intra-arterial (IA) infusion of vasoactive agents and/or balloon angioplasty [1-5].

Aneurysm treatment

Aneurysm rupture was typically managed within twenty-four hours from admission with surgical clipping or endovascular coiling. Patients were monitored in a neurocritical care unit following initial management of the ruptured aneurysm. In the neurocritical care unit, all patients are kept euvolemic. In the event of clinical vasospasm (acute alteration of mental status, new focal neurologic deficits or both) patients are treated with iatrogenic hypertension. This is achieved by increasing the rate of intravenous fluid administration, replacement of patient's measured fluid output with an equal amount of intravenous fluid, and/or the administration of intravenous vasoactive agents to induce hypertension. If the patients are still symptomatic, intraarterial verapamil or nicardipine and/or balloon assisted angioplasty is performed. If the patients develop recurrence of clinical vasospasm, the aforementioned procedure is repeated.

Baseline characteristics

Demographic data was collected via chart review and included age, sex, history of hypertension, history of diabetes mellitus, and tobacco use history. Initial clinical severity was assessed using Hunt-Hess (HH) grading and initial radiologic severity was recorded using the modified Fisher (mF) score. For the statistical analyses, HH grade was dichotomized into low grade [1-3] or high grade [4,5] and mF grade was dichotomized into low grade [1,2] or high grade [3,4]. Hematologic variables recorded on day of admission included white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts. Neutrophil-to-lymphocyte ratios (NLR) were then calculated. These variables were also obtained on day of initial vasospasm.

Aneurysm characteristics

Aneurysm location was determined after imaging review and ascribed to one of the following locations: internal carotid (ICA), middle cerebral (MCA), anterior cerebral (ACA), anterior communicating (Acomm), posterior cerebral (PCA), posterior communicating (Pcomm), basilar (BA), vertebral (VA), or posterior inferior cerebellar (PICA) arteries. For the analyses, location was dichotomized into either anterior (ICA, MCA, ACA, or Acomm) or posterior circulation (PCA, Pcomm, BA, VA, or PICA). Aneurysm treatment (microsurgery or endovascular intervention) and use of external ventricular drain and its duration of placement were also recorded.

Vasospasm characteristics

Vasospasm data collected included time from SAH to vasospasm onset in days (SAH occurring on day 0); severity of vasospasm, defined as mild (0-33% decrease in arterial diameter), moderate (34-66% decrease), or severe (greater than or equal to 67% decrease) based on results of arteriogram; location of vasospasm (anterior or posterior circulation): distribution (unilateral or bilateral), and treatment of vasospasm dichotomized to IA infusion only or balloon angioplasty (alone or in combination with IA infusion).

Statistical analysis

Univariate comparisons of the study variables were made using the independent t-test for continuous variables or the $\chi 2$ test for categorical variables (Fisher exact test if any cell count was <5). Multivariable logistic regression models were created to identify independent predictors of vasospasm retreatment using independent variables with $p < 0.10$ from the univariate analysis. Statistical significance for analysis was determined at a p-value <0.05.

Results

The study cohort was comprised of sixty-nine patients who underwent endovascular treatment of vasospasm following aSAH. Baseline characteristics, disease severity, aneurysm and vasospasm characteristics and outcome data for the entire cohort as well as single versus repeat endovascular treatment groups are shown in **Table 1**. The mean age was 52.5 ± 11.9 years and 33% were male. A history of hypertension was noted in 58%, diabetes mellitus in 10%, and a tobacco use history in 58%. Aneurysms were located in the anterior circulation in 78%. Twenty-seven patients were treated with microsurgical clipping and forty-two were treated with endovascular coiling. HH grades on admission were considered high [4,5] in 36% and mF grades were high [3,4] in 78% on admission. External ventricular drains were used in 86% of patients with a mean duration of 15.8 days. The mean length of hospital stay was 23.9 days.

Table 1: Descriptive results for study cohort and comparison of sub-groups without and with repeat endovascular treatments as a function of patients requiring repeat endovascular treatment of vasospasm.

Variables	Total (n=69)	No Repeat Treatment (n=40)	Repeat Treatment (n=29)	p-value
Age, mean (SD)	52.5 (11.9)	53.0 (11.9)	51.6 (12.0)	0.63
Male Sex, n (%)	23 (33)	14 (35)	9 (31)	0.73
Risk Factors, n (%)				
Hypertension	40 (58)	24 (60)	16 (55)	0.68
Diabetes	7 (10)	2 (5)	5 (17)	0.09
Tobacco Use (Current/Former)	40 (58)	23 (58)	17 (59)	0.93
Admission Blood Pressure (SD)				
Systolic	146.4 (20.0)	150.0 (20.4)	140.0 (18.3)	0.47
Diastolic	84.3 (16.8)	84.8 (16.7)	83.6 (17.0)	0.76
Mean Arterial Pressure	105.2 (15.1)	106.0 (15.7)	103.0 (14.2)	0.33
Admission Hematologic Variables				
White Blood Cells (n=69)	14.3 (5.0)	14.2 (5.0)	14.3 (5.2)	0.91

Neutrophil Count (n=64)	11.7 (4.7)	11.6 (4.6)	11.8 (5.0)	0.87
Lymphocyte Count (n=64)	1.4 (0.8)	1.3 (0.6)	1.6 (0.9)	0.17
Neutrophil-to-Lymphocyte Ratio (n=64)	10.6 (8.4)	10.8 (6.9)	10.3 (10.1)	0.84
Monocyte Count (n=64)	0.7 (0.3)	0.7 (0.4)	0.6 (0.3)	0.37
Platelet Count (n=69)	258.4 (74.3)	252.1 (62.6)	267.0 (88.4)	0.41
Admission Blood Glucose, µg/dL (SD)	155.1 (36.5)	157.7 (46.4)	161.7 (37.2)	0.71
Hunt-Hess Grade				
1-3	44 (63.8)	28 (70)	16 (55)	
4-5	25 (36.2)	12 (30)	13 (45)	0.21
Modified Fisher Grade				
0-2	15 (21.7)	8 (20)	6 (21)	
3-4	54 (78.3)	32 (80)	22 (79)	0.89
Aneurysm Location				
Anterior Circulation	54 (78.3)	34 (85)	20 (69)	
Posterior Circulation	15 (21.7)	6 (15)	9 (31)	0.11
Aneurysm Treatment				
Microsurgical Clipping	27 (39.1)	16 (40)	11 (38)	
Endovascular Coiling	42 (60.9)	24 (60)	18 (62)	0.86
External Ventricular Drain				
Present	59 (85.5)	34 (85)	24 (86)	0.89
Mean Duration, Days	15.8 (5.8)	14.8 (4.8)	17.1 (6.9)	0.14
Time from SAH to Vasospasm, Days	5.8 (3.0)	6 (5)	4 (3)	0.002
Vasospasm Type				
Symptomatic	52 (75.4)	27 (68)	25 (86)	
Radiographic Only	17 (24.6)	13 (32)	4 (14)	0.08
Vasospasm Severity				
Mild	17 (24.6)	12 (30)	8 (28)	0.83
Moderate	21 (30.4)	20 (50)	13 (45)	0.67
Severe	31 (44.9)	14 (35)	17 (59)	0.05
Vasospasm Location				
Anterior Circulation	52 (75.4)	32 (80)	20 (69)	0.32
Posterior Circulation	1 (1.4)	0 (0)	1 (3)	0.24
Both	16 (23.2)	8 (40)	8 (28)	0.46
Vasospasm Treatment				
Angioplasty (Alone or with IA Infusion)	19 (27.5)	12 (30)	7 (24)	
IA Infusion Only	50 (72.5)	28 (70)	22 (76)	0.79
Vasospasm onset Hematologic Variables (SD)				
White Blood Cell Count (n=69)	14.9 (5.4)	15.3 (6.1)	14.4 (4.4)	0.53
Neutrophil Count (n=55)	11.4 (4.5)	11.5 (5.2)	11.2 (3.6)	0.79

Lymphocyte Count (n=55)	1.8 (0.9)	1.5 (0.6)	2.2 (1.2)	0.01
Neutrophil-to-Lymphocyte Ratio (n=55)	7.2 (3.8)	8.1 (4.0)	5.9 (3.1)	0.03
Monocyte Count (n=55)	1.2 (0.6)	1.2 (0.6)	1.3 (0.5)	0.5
Platelet Count (n=69)	298.2 (116.4)	313.4 (127.4)	277.3 (97.4)	0.21
Length of Stay, Days, Mean (SD)	23.9 (9.6)	22.0 (8.5)	26.4 (10.5)	0.06

Vasospasm characteristics and subsequent treatments are shown in **Table 1**. The mean time from onset of SAH to vasospasm was 5.8 days. Vasospasm was clinically symptomatic in 52 patients (75%). Severity of vasospasm was mild in 17 (25%), moderate in 21 (30%), and severe in 31 (45%) patients. IA vasodilator therapy alone was used in 50 (73%) patients and angioplasty alone was used in 2 (3%) patients while combined treatment was used in 17 (25%) patients.

Repeat treatment was performed in 29 patients (42%). On univariate analysis, symptomatic vasospasm (86% *vs.* 68%); p=0.075), shorter time to initial vasospasm (5 *vs.* 6); p=0.002), severe vasospasm (59% *vs.* 35%); p=0.052) and higher absolute lymphocyte count at the time of vasospasm (1.97 *vs.* 1.40); p= 0.008) were associated with repeat treatment (p <0.1). On multivariable logistic regression analysis, only shorter time to initial vasospasm (OR=0.68, 95% CI=0.51—0.91) and higher absolute lymphocyte count at the time of initial vasospasm (OR=2.58, 95% CI=1.04-6.38) remained significant predictors of repeat endovascular treatment **(Table 2)**.

Table 2: Multivariate association with outcome: Logistic regression analysis.

Outcome Variables	Independent Variable	95% C.I.	β	P-value
	Vasospasm Lymphocyte Count	1.04 - 6.38	2.58	0.04
	Symptomatic Vasospasm	0.45 -11.94	2.33	0.312
	Time to Vasospasm, Days	0.51 - 0.91	0.68	0.011
Repeat Endovascular Treatment	Vasospasm Severity, Severe	0.71 - 10.89	2.78	0.143

Discussion

To our knowledge, no prior studies have explored hematologic variables as predictors of endovascular re-treatment. In our cohort of patients with vasospasm undergoing endovascular intervention, higher absolute lymphocyte count at the onset of vasospasm was associated with repeat endovascular treatment. Higher lymphocyte counts at vasospasm onset might imply a more robust transition from acute to chronic inflammation and consequently higher propensity for continued vasospasm [5,6]. This transition is thought to occur days to weeks after the onset of acute inflammation and may explain why lymphocyte count on admission immediately following aneurysm rupture was not associated with re-treatment.

We also found that earlier onset of vasospasm was independently associated with increased odds of re-treatment. Sokolowski et al. found a similar trend towards increased odds of re-treatment with earlier onset of vasospasm on univariate analysis; although this did not reach the threshold for statistical significance in their multivariable model, a OR 0.880/day (95% CI: 0.772 - 1.004, p=0.057) [7].

The modality of initial vasospasm treatment, intra-arterial infusion only versus angioplasty alone or combined, did not impact the rate of re-treatment in our study. This contrasts with prior reports of intra-arterial infusion being associated with increased re-retreatment rates compared with angioplasty alone. This may stem partly from unmeasured bias due to different practice patterns across the studies. For instance, in Sokolowski et al. a sizable group of clinically asymptomatic patients (65%) underwent endovascular intervention for vasospasm, resulting perhaps from the practice of routine catheter angiography 7 days post-rupture in their cohort. The current study had a much smaller percentage of asymptomatic vasospasm (25%) mostly identified by TCD monitoring, but these patients were not taken for endovascular retreatment. Chalouhi et al. and Jun et al. had no patients with asymptomatic vasospasm since intervention was only performed on symptomatic cases refractory to medical therapy [8,9]. Moreover, the indications for re-treatment may be operator dependent even within centers and cannot be accounted for.

There has been recent interest in the use of neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker predicting outcome in various diseases including intracerebral hemorrhage and myocardial infarction [10,11]. Higher NLR has been associated with symptomatic vasospasm and functional outcome in aSAH as well [12,13]. In our restrictive cohort of patients undergoing endovascular treatment however, it was lower NLR at vasospasm onset that seemed to predict re-treatment **(Table 1)**. Since there was no statistical difference in neutrophil counts on univariate analysis, differences in NLR

were felt to be driven entirely by the lymphocyte counts **(Table 1)**. NLR was therefore excluded from multivariable models that already adjusted for lymphocyte count to avoid collinearity.

Limitations of the study include its single-center retrospective design and small cohort size. The sample size in the multivariable model for re-treatment was reduced to 52 due to missing differential white cell counts. Medical complications like infection/ sepsis, organ failure, malignancy which can confound the relationship between hematologic variables and retreatment could not be accounted for. Another unmeasurable but important variable is treating physician preference for performing intervention or repeat intervention. Despite these limitations, the study is the first to describe associations between hematologic parameters and retreatment of recurrent and/or refractory cerebral vasospasm.

Conclusion

Elevated lymphocyte count at the onset of vasospasm in patients requiring treatment for cerebral vasospasm may be indicative of a predisposition to vasospasm recurrence. The monitoring of lymphocyte count would be a novel approach to the early identification of recurrent vasospasm and improve selection of patients who may require retreatment.

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