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Factors Associated with the Development of Anemia After Subarachnoid Hemorrhage

Tomoko R. Sampson, Rajat Dhar, and Michael N. Diringer

Department of Neurology, Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8111, Saint Louis, MO 63110, USA

Abstract

Introduction—Anemia is common after subarachnoid hemorrhage (SAH) and may exacerbate the reduction in oxygen delivery that underlies delayed cerebral ischemia. Fall in hemoglobin may relate to blood loss as well as inflammatory suppression of erythropoiesis. Identifying factors associated with anemia may facilitate targeted interventions, such as the use of erythropoiesis-stimulating agents, which could minimize the burden of anemia and reduce red blood cell (RBC) transfusion requirements.

Methods—We analyzed a cohort of patients with spontaneous SAH admitted over a 3-year period who survived at least 4 days. All patients had daily hematocrit values drawn while in the ICU. Multivariate regression was performed to determine baseline and early post-admission variables associated with development of anemia (defined as hematocrit < 30%).

Results—Anemia developed in 47% of 243 patients with SAH after a mean of 3.5 days (median 2 days). Admission variables independently associated with anemia were female gender (OR 3.7, 95% CI 1.8–7.6), baseline hematocrit < 36% (OR 3.9, 1.5–10.1 compared to 36–45%), history of hypertension (OR 2.1, 1.05–4.2), and poor clinical grade (OR 5.9, 2.3–15.0). Surgical aneurysm treatment (OR 13.5, 6.0–30.3) and greater admission SIRS score (OR 5.7, 1.7–19.2 if 3–4 criteria for systemic inflammatory response syndrome were met on day of admission compared to none) were also associated with fall in hematocrit.

Conclusions—It may be possible to predict those most likely to develop anemia using simple baseline clinical variables. Anemia was strongly related to surgery, likely through greater blood loss, and greater systemic inflammatory response on admission, possibly explained by cytokine-mediated inhibition of RBC production.

Keywords

Subarachnoid hemorrhage; Anemia; Systemic inflammatory response syndrome; Intracranial aneurysm

Introduction

A major source of preventable morbidity after aneurysmal subarachnoid hemorrhage (SAH) is delayed cerebral ischemia (DCI) [1]. This secondary brain injury results from impaired cerebral oxygen delivery, associated with vasospasm and a reduction in cerebral blood flow [2]. A fall in hemoglobin level may further impair oxygen delivery to vulnerable brain regions. Anemia occurs commonly after SAH, with hemoglobin falling below 10 g/dl in 39–57% of

these critically ill patients [3,4]. Lower hemoglobin has been associated with poor outcomes in patients with SAH, including a higher rate of cerebral infarction [5-7].

Despite increasing interest in the contribution of anemia to DCI and poor outcome, there has been little evaluation of the factors associated with developing anemia in this population. Identifying those at highest risk may allow early interventions targeted at preventing a potentially harmful fall in hemoglobin, such as the use erythropoiesis-stimulating agents (ESAs) or a more aggressive transfusion strategy. To achieve this goal, we retrospectively analyzed a prospectively collected cohort of SAH patients to determine risk factors (available at or shortly after admission) for the development of anemia during their ICU stay.

Methods

Subjects

All patients diagnosed with SAH at our institution are admitted to the Neurology/Neurosurgery Intensive Care Unit (NNICU) for stabilization and management. They remain in the NNICU until risk of complications such as hydrocephalus and vasospasm have abated, usually for at least 10–14 days. Data on patients cared for in this unit are prospectively entered into a computerized database (QUiC, Space Labs) by a trained research nurse utilizing strict definitions and guidelines.

We evaluated all patients with SAH admitted over a 3-year period (December 2002–December 2005). Patients were eligible if they were admitted within 4 days of SAH, confirmed by imaging or lumbar puncture. They were excluded if there was a history of trauma or if a vascular malformation or other non-aneurysmal source of bleeding was discovered. Patients dying within the first 4 days after admission were also excluded, as these severely affected patients (71% were poor grade) would not have equivalent opportunity to develop anemia and usually had aggressive treatments limited. Patients staying in the ICU less than 24 h were similarly excluded. The Washington University *Human Research Protection Office* approved the use of previously collected data for this analysis; a waiver for individual patient consent was obtained.

Ruptured aneurysms were secured surgically or by endovascular means, usually within 24 h of admission. Nimodipine was administered to all patients. A euvolemic state was maintained by careful monitoring of fluid intake and output, but prophylactic hemodynamic augmentation was not employed. Anemia was generally tolerated unless hemoglobin fell below 7 g/dl, while some patients were transfused if hemoglobin was 7–10 g/dl in the presence of vasospasm or DCI.

Data Collection

The following variables were extracted from the database for this analysis: demographics including age, gender, race, and history of hypertension, smoking, diabetes mellitus, and coronary artery disease. Admission status was evaluated using the World Federation of Neurological Surgeons (WFNS) grading scale [8]; WFNS IV or V was considered poor grade. Extent of hemorrhage was graded on all available admission CT scans using the Fisher scale [9]. We also recorded presence of hydrocephalus requiring ventriculostomy, and respiratory failure requiring intubation on admission. All patients had daily blood counts, from which hematocrit was prospectively extracted into the ICU database (hemoglobin was not prospectively collected). Other variables collected included surgical vs. endovascular aneurysm treatment and elevation of serum troponin within 24 h of admission. The presence of the systemic inflammatory response syndrome (SIRS) was evaluated on the day of admission and considered present if two or more of the standard criteria were met [10]: Heart rate > 90 beats/min; respiratory rate > 20 breaths/min; leukocyte count <4,000 or >12,000; and

temperature >38 or $<36^{\circ}\text{C}$. The number of SIRS criteria met on admission was also measured. Symptomatic vasospasm was defined by the presence of new or worsening neurological deficits associated with angiographic vasospasm, after excluding other causes.

Analysis

We defined anemia as hematocrit $< 30\%$ (approximately hemoglobin level < 10 g/dl) occurring between days 1 and 14 of ICU stay, or prior to ICU discharge. We also measured ICU and hospital length of stay (LOS) and hospital discharge disposition (home, rehabilitation facility, long-term care) and mortality. Data was exported from the QUiC database into SPSS (version 12) for analysis. Baseline factors were analyzed in relationship to development of anemia using logistic regression and variables with $P < 0.10$ were entered into a backward stepwise analysis using multivariate logistic regression. Fisher grade was not included in the final model because admission CT scans were not available for 25% of patients (when performed at outside facilities) and its inclusion would have excluded all these patients.

Results

Of 368 patients diagnosed with SAH over the 3-year study period, 243 were eligible for analysis. The remainder was excluded based on: prolonged or unknown duration from ictus (49), non-aneurysmal or traumatic SAH (43), death within 4 days (31), or ICU stay <24 h (2). 90% of included subjects were admitted within 24 h of symptom onset. Median ICU LOS was 12 days (inter-quartile range 5–18), with 60% of the group having hematocrit data over at least 7 days.

Mean admission hematocrit was $39.8 \pm 5\%$. Anemia ($\text{Hct} < 30\%$) developed in 114 patients (47%) and 47 patients (19%) received at least one red blood cell (RBC) transfusion in the ICU (including 39% of anemic patients). A significantly greater proportion of those developing anemia had baseline hematocrit below 36% and anemia was rare in those admitted with hematocrits over 45% (Table 1). The mean drop in hematocrit from admission to nadir was $9 \pm 7\%$ (approximately 3 g/dl). The steepest drop occurred over the first 4 days, with the rate of drop averaging 2.4% per day over this period in those developing anemia compared to 1.1% in those not. Mean time to develop anemia in those 114 patients was 3.5 days, with a median of only 2 days.

Multivariate analysis (Table 2) found that female gender, history of hypertension, baseline hematocrit less than 36%, and poor clinical grade were independently associated with developing anemia; admission hematocrit over 45% was protective. However, the event most powerfully associated with anemia was undergoing aneurysm surgery, with an adjusted odds ratio of 13.5. While the simple presence of SIRS on admission did not confer an independently elevated risk of anemia, meeting a greater number of SIRS criteria (SIRS score) on admission was independently associated with anemia. SIRS score and surgery were also the two variables most strongly associated with drop in hematocrit from admission to nadir (model not shown). The difference in the rate of developing anemia is compared between those undergoing surgery and those receiving endovascular or no aneurysm treatment in Fig. 1.

Discussion

In this analysis of a large cohort of patients with spontaneous SAH, we found that almost half developed anemia (hematocrit $< 30\%$) at some point during their ICU stay, often quite soon after admission. This high frequency of anemia is in keeping with other studies in patients with SAH [3,4], reminding us of the significance of this medical complication of critical illness [11]. We found that certain admission variables predicted anemia, including female gender, lower baseline hematocrit level ($<36\%$, hemoglobin under 12 g/dl), and poor clinical status.

Knowledge of such easily available factors may allow risk stratification on admission and early interventions in those most likely to develop anemia. For example, males with good grade SAH and a baseline hematocrit over 45% are very unlikely to develop significant anemia based on our model. A female with a low baseline hematocrit undergoing surgery is, conversely, at very high-risk.

Anemia in critically ill patients results from a combination of factors, predominantly losses through surgery and frequent phlebotomy, as well as impaired bone marrow production of RBCs. We have demonstrated that similar processes likely conspire to cause anemia in patients with SAH. Aneurysm surgery can be a potent source of blood loss (for example, with intraoperative aneurysm rupture), but can also promote systemic inflammatory activation post-operatively [12]. “Anemia of acute disease” relates to a blunting of the bone marrow response to erythropoietin [13,14], mediated by inflammatory cytokines such as interleukin-1 and tumor necrosis factor [15]. Subarachnoid hemorrhage is known to induce a systemic inflammatory response associated with elevated levels of cytokines [16,17]. The clinical manifestations of this process are reflected in the SIRS criteria measured in this study [10]. We and others have shown that SIRS is present in a majority of patients early after SAH, even in the absence of infectious triggers [12,18]. In this study, we found that higher SIRS score on admission was associated with fall in hematocrit below 30% and extent of drop from baseline. This supports a relationship between activation of a vigorous inflammatory response and the pathogenesis of anemia in this setting.

Understanding the factors associated with development of anemia after SAH might help direct therapies to blunt the frequent fall in hemoglobin. Avoiding surgery for aneurysms amenable to endovascular approaches might minimize this complication. We have now shown that SIRS is associated with both anemia and vasospasm, highlighting the role of inflammation in both these interrelated disorders. While no therapies have been proven to blunt the systemic inflammatory response after SAH, statins have a theoretical basis to achieve this goal [19]. Statins have been shown to blunt SIRS activation after cardiac surgery [20], and have shown promise in modulating inflammation in animal models of SAH [21]. Based on our preliminary results, it may be worthwhile to compare the incidence of anemia within randomized trials comparing statin therapy to placebo for prevention of vasospasm after SAH to further test this hypothesis.

The use of erythropoiesis-stimulating agents (e.g., recombinant erythropoietin) to overcome the marrow resistance associated with critical illness and SIRS might avoid the need for subsequent transfusion, as some studies have demonstrated in general ICU patients [22,23]. Given the recognized risks of transfusion [24], including an increased rate of vasospasm in one study [25] and an association with worse outcome in another [4], strategies to minimize the need for this intervention may be warranted in patients with SAH. Erythropoietin may also have neuroprotective properties in SAH, including ischemic preconditioning and augmentation of nitric oxide production [26,27]. A recent randomized human trial of recombinant erythropoietin in SAH demonstrated a significant reduction in TCD-defined severe vasospasm and delayed ischemic deficits [28]. Transfusion requirements were also reduced (30% vs. 10%, $P = 0.048$), although hematocrit was not different between groups. Further study is required to define the role of such agents in preventing anemia as well as cerebral ischemia. As we found that the drop in hemoglobin occurred early after admission for patients with SAH (within 4 days in most), this may be too soon for erythropoietin to significantly prevent anemia. However, if treatment can reduce ischemic injury and prevent further drops in hemoglobin requiring transfusion, it may play an important role in the management of SAH.

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Fig. 1.
Survival curve of incidence and time to develop anemia by intervention

Table 1

Comparison between patients developing and those not developing anemia

Variable	Anemia (n = 114)	No anemia (n = 129)	Univariate OR	95% CI	P-value
Age, years (mean ± SD)	57.6 ± 13.9	53.1 ± 11.5	1.03	1.008–1.05	0.007
Race: White	71 (63%)	100 (78%)			
African-American	37 (33%)	27 (21%)	1.93	1.08–3.45	0.027
Sex: female	90 (79%)	63 (49%)	3.93	2.23–6.93	<0.001
Medical history					
Hypertension	62 (54%)	50 (39%)	1.88	1.13–3.14	0.015
Diabetes mellitus	13 (11%)	7 (5%)	2.24	0.86–5.84	0.098
Smoking	33 (29%)	39 (30%)	0.94	0.54–1.63	0.83
CAD	7 (6%)	7 (5%)	1.14	0.39–3.36	0.82
WFNS grade IV–V	41 (36%)	15 (12%)	4.27	2.21–8.26	<0.001
Fisher grade: 3 ^a	60 (60%)	33 (40%)	2.23	1.23–4.04	0.008
SIRS present on admission	69 (61%)	54 (42%)	2.1	1.3–3.6	0.004
SIRS score on admission	1.75 ± 1.1	1.28 ± 1.0			0.001
1 criteria met	32 (28%)	45 (35%)	1.56	0.73–3.35	
2 criteria met	39 (34%)	35 (27%)	2.45	1.14–5.25	
3–4 criteria met	28 (25%)	16 (12%)	3.85	1.62–9.15	
Hydrocephalus	82 (72%)	44 (34%)	4.95	2.86–8.56	<0.001
Respiratory failure on admission	57 (50%)	26 (20%)	3.96	2.25–6.97	<0.001
Baseline hematocrit (%)	38.6 ± 5.0	40.9 ± 4.7	0.90	0.85–0.95	<0.001
<36%	28 (25%)	14 (11%)	2.37 ^b	1.16–4.84	
>45%	10 (9%)	29 (23%)	0.26 ^b	0.19–0.93	
Aneurysm treatment					
None	4 (4%)	31 (24%)	4.91 ^c	2.84–8.47	<0.001
Surgery	81 (71%)	43 (33%)			
Endovascular	29 (25%)	55 (43%)			
Troponin elevation	44 (39%)	17 (13%)	4.14	2.20–7.81	<0.001
ICU LOS (median, IQR)	16 (14–22)	5 (3–12)			<0.001
Symptomatic vasospasm	48 (42%)	16 (12%)	5.14	2.70–9.76	<0.001

Variable	Anemia (n = 114)	No anemia (n = 129)	Univariate OR	95% CI	P-value
Mortality	14 (12%)	3 (2%)	5.88	1.64–21.0	0.006
Discharged home	22 (18%)	85 (58%)	0.12	0.07–0.22	<0.001

SD Standard deviation, WFNS World Federation of Neurological Surgeons, SIRS systemic inflammatory response syndrome, LOS length of stay, IQR inter-quartile range

^aFisher grades available for only 182 patients
^bCompared to baseline hematocrit 36–45%
^cSurgery compared to endovascular or none

Table 2

Final multivariate model

Variable	Multivariate OR	95% CI
Sex: female	3.67	1.78–7.55
History of hypertension	2.09	1.05–4.15
WFNS grade IV–V	5.91	2.33–14.99
SIRS score on admission ^a		
1 criteria met	2.28	0.84–6.16
2 criteria met	2.54	0.92–6.99
3–4 criteria met	5.65	1.66–19.2
Baseline hematocrit ^b		
<36%	3.91	1.51–10.12
>45%	0.26	0.09–0.71
Surgical treatment	13.53	6.04–30.27

^a Compared to no criteria met

^b Compared to baseline hematocrit 36–45%