Original Contribution

Anemia After Aneurysmal Subarachnoid Hemorrhage Is Associated With Poor Outcome and Death

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Background and Purpose—Anemia after aneurysmal subarachnoid hemorrhage is common and potentially modifiable. Here, we first evaluate the effect of anemia on neurological outcome and death and second, study the effects of packed red blood cell transfusion on outcome.

Methods—A secondary analysis on 413 subjects in the CONSCIOUS-1 study (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage). Multivariable logistic regression identified independent risk factors for anemia and determined the effect of anemia on neurological outcome and death, while adjusting for selected covariates. Optimal predictive thresholds for hemoglobin levels were determined using receiver operating characteristic curve analysis. Finally, patients were pseudorandomized to transfusion using propensity score matching to study the effect of transfusions on outcome.

Results—Anemia, defined as hemoglobin <10 g/dL, was present in 5% of patients at presentation, in 29% of patients after aneurysm securing (days 1–3), and in 32% of patients during the peak delayed cerebral ischemia risk period (days 5–9). Anemia after aneurysm securing (odds ratio, 1.96; 95% confidence interval, 1.07–3.59; P=0.03) and during the delayed cerebral ischemia window (odds ratio, 2.63; 95% confidence interval, 1.46–4.76; P=0.0014) was independently associated with poor neurological outcome. Anemia postaneurysm securing (odds ratio, 3.50; 95% confidence interval, 1.15–10.62; P=0.027) but not during the delayed cerebral ischemia window was associated with death. Using propensity score-matched cohorts, we found that transfusion of anemic patients did not improve long-term outcome (P=0.8) or mortality rates (P=0.9). Transfusion of patients with a hemoglobin concentration >10 g/dL was associated with improved neurological outcomes (odds ratio, 0.09; 95% confidence interval, 0.002–0.72; P=0.015), with no differences in mortality.

Conclusions—Anemia after aneurysmal subarachnoid hemorrhage is associated with poor long-term neurological outcome and death. Transfusion of packed red blood cells is beneficial for patients who are not considerably anemic beforehand, suggesting further work needs to define the threshold but also the time period of anemia that is sufficient and necessary to contribute to poor outcomes.

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Advances in the initial treatment of ruptured intracranial aneurysms have led to decreased mortality rates[1] and improved outcomes,[2] which has shifted the emphasis from aneurysm repair to mitigating secondary injuries in a critical care setting. Patients affected by aneurysmal subarachnoid hemorrhage (aSAH) face a multitude of medical complications ranging from vasospasm and hydrocephalus to severe inflammatory reactions and anemia, contributing to poor outcomes.[3,4]

Anemia negatively impacts cerebral oxygenation[5] and is potentially modifiable with blood transfusions; however, the enthusiasm to transfuse such patients must be tempered by the potential harms. Data from the TRICC trial (Transfusion Requirements in Critical Care)[6] demonstrated that a restrictive transfusion threshold (<7 g/dL) is associated with decreased mortality, and additional studies examining patients without neurological conditions have shown that a restrictive threshold is associated with improved outcomes or fewer adverse events.[7–9] However, these data are contradicted by evidence from patients with neurological illnesses, who were underrepresented in the TRICC trial. Anemia after aSAH has been associated with death and poor neurological outcome.[10–14] Furthermore, higher

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hemoglobin concentrations after aSAH have been associated with improved outcomes.[12,13]

Despite the increasingly recognized correlations between anemia and poor outcomes, transfusion therapy after aSAH remains controversial. The use of transfusions has yielded mixed results with either no benefit[14] or an association with poor outcomes.[13] Furthermore, past studies examining the role of transfusions after aSAH have not taken into account that blood transfusions in critically ill patients can often be an independent risk factor for poor outcomes.[13,14] To complicate matters further, the interpretation of past studies remains challenging because of the fact that many were derived from historical cohorts[13,14] where aneurysms may have been treated in a delayed fashion. Others were derived from retrospective data, imposing significant limitations on conclusions that could be drawn.[10,11]

In the current study, we examined the association between anemia and neurological outcomes in patients who were enrolled in the CONSCIOUS-1 study[15] (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage). Unique insights can be gleaned from this data set because it represents prospectively collected data, accrued with the rigor of a randomized controlled trial with 413 patients from multiple centers. Importantly, within this data set, hundreds of variables were collected, meticulously describing hemoglobin trends, in addition to numerous potentially confounding covariates. We apply relevant methodology, such as multivariable modeling and propensity score matching, to balance selected covariates and provide a detailed account of the effects of anemia and transfusions on patient outcome.

Methods

Study Population

Data were derived from 413 subjects who were enrolled within 48 hours after aSAH into the CONSCIOUS-1 study, as described previously.[15–17] Ethics approval was not required because all data were anonymous from a previously created database. Data is available on request from the corresponding author.

Clinical Assessment

Patients with a CT-confirmed aSAH were enrolled. Initial symptoms were classified according to the World Federation of Neurological Surgeons (WFNS) scale.[18] Long-term neurological outcome was assessed with the extended Glasgow outcome scale (eGOS) at 12 weeks after aSAH.[19] Unfavorable long-term neurological outcome was defined as death or disability worse than moderate disability (eGOS, <5). Delayed ischemic neurological deficits (DIND) was defined as angiographic vasospasm associated with a decline in neurological status lasting >2 hours and with other causes being ruled out. Neurological decline was defined as a 2-point decrease on the Glasgow coma scale score or an increase of 2 points on the National Institutes of Health stroke scale.[20]

Radiology

The Hijdra scale[21] was used to quantify the subarachnoid clot burden, and intraventricular hemorrhage was quantified with the modified Graeb score.[22,23] Each patient underwent catheter angiography within 48 hours of aneurysm rupture and again between 7 and 11 days post-aSAH. Angiographic vasospasm was quantified by the difference in the diameter of large proximal arteries by comparing baseline and follow-up angiography (classified as none/mild, 0%–33%; moderate, 34%–66%; and severe, 67%–100%).

Hemoglobin Measurements

The hemoglobin at presentation, as well as the nadir hemoglobin postprocedure and in the delayed cerebral ischemia (DCI) risk period, was extracted. In an attempt to quantify both the magnitude and duration of low hemoglobin, we also created a single composite variable defined as hemoglobin-deficit days. To do this, we considered normal hemoglobin to be 13.0 and 12.0 for men and women, respectively, based on the lower limit of normal for the Medical Council of Canada normative ranges. The cumulative discordance from these ranges for 3 days postprocedure or within the DCI risk period was calculated. For example, a man with a hemoglobin of 12 for 2 days and 13 for the third would have a hemoglobin-deficit days value of −2.

Statistical Analysis

Data are presented as mean±SD or median with interquartile range, where stated. The primary outcomes of interest were the differences in clinical outcome (eGOS) and mortality between patients with a nadir hemoglobin concentration <10 g/dL and those with hemoglobin ≥10 g/dL. A hemoglobin threshold of 10 g/dL was chosen because this has been selected by other groups studying anemia after aSAH, as well as found to be associated with outcome.[14,24] The secondary outcome was the impact of transfusions of packed red blood cells on death and long-term outcome. Differences in demographic and clinical factors were initially compared using the Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. Univariate statistics with a significance level <0.2 were then entered into a multivariable logistic regression model as described previously,[25] to determine covariates of anemia at different time points. The differences in outcome on the eGOS and death between patients with Hb <10 and ≥10 g/dL were compared using univariate linear regression analysis at 3 time points: at hospital admission (day 0 of aneurysm rupture and before aneurysm securing), postaneurysm securing (days 1–3 postaneurysm securing), and during the peak DCI window (days 5–9). The effect of anemia on long-term outcomes on the eGOS and death was evaluated using a multivariable logistic regression. Previously identified predictors of outcome from prior analyses based on the CONSCIOUS-1 study[17,26] and those previously identified as independent prognostic factors for poor outcome after aSAH[27] were included in the multivariable logistic regression. These included hypertension, WFNS scores on admission (dichotomized as WFNS IV and V versus I–III), subarachnoid clot burden, intraventricular hemorrhage, and angiographic vasospasm (none/mild versus moderate/severe). To assess the effect of perioperative complications (including intraoperative aneurysm rupture) on postoperative anemia after aneurysm clipping, previously identified complications[16] were entered into a multivariable logistic regression with Hb <10 g/dL as the dependent variable.

Because patients in this study cohort were not randomized to receive blood transfusions, we used propensity score matching to examine the effect of packed red blood cell transfusions on long-term outcome and death. Subjects were matched for age, sex, nicotine use, history of hypertension, preexisting heart conditions, WFNS scores at admission, aneurysm location, aneurysm size, Hijdra score, intracerebral hemorrhage, and intraventricular hemorrhage. Propensity score matching was performed by using calipers with a width of 0.3, as reported previously.[16] The distribution of propensity scores is presented in the online-only Data Supplement. Additional propensity matching on a subset of patients during the DCI window with a hemoglobin level between 9.01 and 10.0 g/dL or 10.0 and 11.0 g/dL was compared to determine whether the beneficial effect of blood transfusions occurred within a limited range. Receiver operating characteristic curve analysis was used to define hemoglobin levels at each of the above specified time points to predict poor clinical outcome on the eGOS and death.[25,28] To further examine whether a dose response of hemoglobin on outcome exists, hemoglobin levels were split into discrete groups of 1 g/dL ranging from <8.0 to >12.1 g/dL

and were analyzed by comparing each threshold to the >12.1-g/dL group with Fisher exact test and Bonferroni correction. For all final models, statistical significance was set at $P<0.05$. Analysis was performed using custom scripts in R statistical software.

Results

Patient Demographic Data

In the CONSCIOUS-1 study, 413 patients were enrolled with a mean age of 51±11 years, and 124 (30%) were men. Demographic and clinical variables are presented in Table 1. Analysis of hemoglobin was separated into 3 time epochs: at presentation to hospital, after aneurysm securing (days 1–3 postaneurysm securing), and during the DCI window (days 5–9). Anemia was present in 5% of patients at presentation (22 of 413), in 29% (118 of 413) of patients postprocedure, and in 32% (133 of 413) of patients during the DCI window. On univariate analysis, female patients during any time point were more likely to be anemic (women with Hb <10 g/dL at presentation: 95.5% [21 of 22] versus women with Hb >10 g/dL at presentation: 69.4% [270 of 389], $P<0.001$; anemia postprocedural women: 83.9% [99 of 118] versus 64.6% [166 of 257], $P<0.001$; DCI window anemia women: 82.7% [110 of 133] versus 64.8% [151 of 233], $P<0.001$; 95% confidence interval [CI], 0.22–0.67). Patients with anemia postprocedurally and during the DCI window were more likely to present with a worse neurological grade (WFNS grade IV and V; postprocedure anemia: 34.4% [43 of 118] versus 18.7% [48 of 257], $P\leq0.001$; DCI window anemia: 32.3% [43 of 133] versus 20.6% [48 of 233], $P=0.017$), have a higher intraventricular clot burden (postprocedure anemia: 3.62±2.69 versus 2.89±2.58, $P=0.0042$; DCI window anemia: 3.69±2.67 versus 2.77±2.57, $P\leq0.001$), and were more likely to have had their aneurysm secured by clipping (postprocedure anemia clipped: 65.3% [77 of 118] versus postprocedure Hb >10 g/dL clipped: 35.4% [91 of 257], $P<0.0001$; DCI window anemia clipped: 55.6% [74 of 133] versus vasospasm window Hb >10 g/dL clipped: 37.3% [87 of 233], $P<0.001$). Patients with anemia during the DCI period were more likely to have moderate-to-severe angiographic vasospasm than patients with Hb >10 g/dL (38.3% [51 of 133] versus 26.2% [55 of 233]; $P=0.018$; Table 1).

Clinical and Radiographic Covariates Associated With Anemia

Significant variables on univariate analysis were entered into a multivariable logistic regression analysis to identify covariates associated with anemia at each of the 3 time points. Female sex was the only covariate associated with anemia at presentation on multivariable analysis (female sex: odds ratio [OR], 8.83; 95% CI, 1.17–66.1; $P=0.035$; intraventricular hemorrhage burden: OR, 1.09; 95% CI, 0.93–1.27; $P=0.3$; intraparenchymal hemorrhage: OR, 0.65; 95% CI, 0.14–3.01; $P=0.6$). On multivariable analysis of anemia postprocedurally, a lower presenting neurological grade (WFNS IV and V; OR, 1.37; 95% CI, 1.09–1.70; $P=0.007$), aneurysm clipping

Table 1. Demographic and Clinical Factors of 413 Patients After Aneurysmal Subarachnoid Hemorrhage*

	At Presentation, Hb<10 (n=22)	At Presentation, Hb>10 (n=389)	*P* Value	Postprocedure, Hb<10 (n=118)	Postprocedure, Hb>10 (n=257)	*P* Value	Delayed Cerebral Ischemia Period, Hb<10 (n=133)	Delayed Cerebral Ischemia Period, Hb>10 (n=233)	*P* Value
Age, y	52.7±9.34	50.9±10.8	0.41	51.7±11.2	50.9±10.9	0.54	52.2±10.8	50.5±11.1	0.15
Men	1 (4.5%)	119 (30.6)	<0.0001	19 (16.1)	91 (35.4)	<0.0001	23 (17.3)	82 (35.2)	<0.001
Nicotine use	13 (59.1%)	203 (52.2)	0.66	55 (46.6)	138 (53.7)	0.43	61 (45.9)	127 (54.5)	0.19
Preexisting hypertension	9 (40.9)	223 (57.3)	0.18	50 (42.4)	105 (40.9)	0.82	57 (42.9)	92 (39.5)	0.58
WFNS score IV and V	6 (27.2)	94 (24.2)	0.79	43 (34.4)	48 (18.7)	<0.001	43 (32.3)	48 (20.6)	0.017
Intraventricular clot presence	2 (9.1)	89 (22.9)	0.19	99 (83.9)	197 (76.7)	0.13	110 (82.7)	181 (77.7)	0.28
Intraventricular clot burden; Graeb score	2.7±2.3	2.9±2.7	0.11	3.6±2.7	2.8±2.6	0.0042	3.7±2.7	2.77±2.6	<0.001
Subarachnoid clot burden; Hijdra score	18.2±6.1	18.3±5.86	0.91	18.6±6.1	18.3±5.9	0.54	18.8±6.2	17.9±5.7	0.08
Vasospasm									
Moderate/severe	6 (27.3)	122 (31.4)	0.82	46 (38.9)	28.8	0.057	51 (38.3)	61 (26.2)	0.018
Clip	10 (45.5)	173 (44.5)	0.9	77 (62.3)	91 (35.4)	<0.0001	74 (55.6)	87 (37.3)	<0.001
Coil	11 (50.0)	201 (51.7)		36 (30.5)	158 (61.48)		55 (41.4)	137 (58.8)	
Aneurysm size, mm									
0–5	7 (31.8)	149 (38.3)	0.65	45 (38.1)	97 (37.7)	0.99	56 (42.1)	85 (36.5)	0.21
>5	14 (63.6)	229 (58.9)		73 (61.9)	155 (60.3)		69 (51.9)	142 (60.9)	

WFNS indicates World Federation of Neurological Surgeons.
*Units in parenthesis represent percentages; error expressed as ±SD.

(OR, 0.24; 95% CI, 0.14–0.40; *P*<0.0001), and female sex were associated with anemia (OR, 3.45; 95% CI, 1.82–6.53; *P*=0.0001). During the DCI window, a higher intraventricular clot burden (OR, 1.12; 95% CI, 1.01–1.24; *P*=0.027), aneurysm clipping (OR, 0.42; 95% CI, 0.26–0.67; *P*<0.001), and female sex (OR, 2.51; 95% CI, 1.42–4.43; *P*=0.001) were associated with anemia (Tables 2 and 3). Because aneurysm clipping was associated with anemia, we analyzed the contribution of perioperative complications, including intraoperative aneurysm rupture, on postoperative anemia. In this data set, no identified complications were associated with anemia after aneurysm clipping, including intraoperative aneurysm rupture (*P*=0.97; Table I in the online-only Data Supplement).

Anemia, Long-Term Outcome, and Death

On univariate analysis, anemia postprocedurally and during the DCI period was associated with unfavorable neurological outcome (postprocedure anemia: OR, 3.43; 95% CI, 2.15–5.48; *P*<0.0001; anemia during DCI window: OR, 3.98; 95% CI, 2.47–6.40; *P*<0.0001) and death (postprocedure anemia: OR, 4.01; 95% CI, 1.71–9.46; *P*=0.0015; anemia during DCI window: OR, 3.79; 95% CI, 1.49–9.66; *P*=0.0051). Anemia at initial presentation was not associated with outcome (OR, 1.07; 95% CI, 0.42–2.69; *P*=0.89) or death (OR, 1.04; 95% CI, 0.84–1.29; *P*=0.65). The number of hemoglobin-deficit days was analyzed for patients during the postprocedure window and during the DCI window. On univariate analysis, the number of hemoglobin-deficit days was associated with unfavorable outcome (postprocedure: 3.52±4.38 deficient days; OR, 0.91; 95% CI, 0.84–0.96; *P*=0.0031; DCI window: 4.46±4.81 deficient days; OR, 0.87; 95% CI, 0.83–0.93; *P*<0.0001) but only death during the DCI window (postprocedure: OR, 0.89; 95% CI, 0.78–1.01; *P*=0.061; DCI window: OR, 0.87; 95% CI, 0.78–0.97; *P*=0.022).

We next examined the contribution of anemia to neurological outcome and death in a multivariable logistic regression model with previously identified independent predictors of outcome and death. On multivariable logistic regression, anemia postprocedurally (OR, 1.96; 95% CI, 1.07–3.59; *P*=0.030) and during the DCI window (OR, 2.63; 95% CI, 1.46–4.76; *P*=0.0014) was independently associated with poor neurological outcome. Other variables associated with unfavorable outcome included severe-to-moderate angiographic vasospasm (OR, 2.52; 95% CI, 1.44–4.44; *P*=0.001), a higher subarachnoid clot burden (OR, 1.07; 95% CI, 1.02–1.12; *P*=0.0089), and a poor presenting clinical grade (WFNS IV and V; OR, 3.56; 95% CI, 1.93–6.53; *P*<0.001; Table 4). Anemia postprocedurally (OR, 3.50; 95% CI, 1.15–10.62; *P*=0.027) but not during the DCI window was an independent predictor of death on multivariable logistic regression. Moderate-to-severe angiographic vasospasm was also associated with death (OR, 1.86; 95% CI, 1.6–4.81; *P*<0.001; Table 5). When the number of gram-deficient days were added into the multivariable model they were not significant independent predictors of outcome (postprocedure: *P*=0.061; DCI window: *P*=0.69).

Anemia postprocedurally and during the DCI window, but not at initial presentation, was significantly associated with longer stays in an intensive care unit (anemia at presentation: 11.3±6.5 days versus nonanemic: 12.7±10.8 days, *P*=0.89; postprocedure anemia: 15.6±9.9 days versus nonanemic: 11.1±10.3, *P*<0.0001; anemia during DCI window: 17.7±12.5 days versus nonanemic: 9.7±7.8 days, *P*<0.0001).

Patients with anemia postprocedurally or during the DCI period had a significantly higher incidence of DIND (anemia with DIND postprocedure: 26.3% [31 of 118] versus 15.9% [41 of 257]; OR, 1.87; 95% CI, 1.06–3.28; *P*=0.024; anemia

Table 2. Multivariable Logistic Regression of Predictors of Anemia Postaneurysm Securing

	OR	95% CI	*P* Value
WFNS	1.37	1.09–1.70	0.007
IVH burden	1.09	0.98–1.20	0.06
Presence of IPH	1.03	0.48–2.18	0.9
Coiling	0.24	0.14–0.40	<0.0001
Sex	3.45	1.82–6.53	0.0001
Vasospasm	1.11	0.66–1.90	0.7

CI indicates confidence interval; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; OR, odds ratio; and WFNS, World Federation of Neurological Surgeons.

Table 3. Multivariable Logistic Regression of Predictors of Anemia During Delayed Cerebral Ischemia Period

	OR	95% CI	*P* Value
WFNS	1.21	0.98–1.49	0.07
IVH burden	1.12	1.01–1.24	0.027
Coiling	0.42	0.26–0.67	<0.001
Sex	2.51	1.42–4.43	0.001
Vasospasm	1.45	0.87–2.32	0.2
Age, y	1.00	0.98–1.03	0.5
SAH clot burden	0.99	0.95–1.04	0.8
Nicotine use	0.79	0.49–1.28	0.3

CI indicates confidence interval; IVH, intraventricular hemorrhage; OR, odds ratio; SAH, subarachnoid hemorrhage; and WFNS, World Federation of Neurological Surgeons.

Table 4. Multivariable Logistic Regression of Long-Term Neurological Outcome on GOSE

	OR	95% CI	*P* Value
Initial sBP	1.00	0.99–1.05	0.25
WFNS	3.56	1.93–6.53	<0.0001
IVH	1.05	0.95–1.17	0.35
Hijdra	1.07	1.02–1.12	0.0089
ICH	1.31	0.60–2.85	0.50
Vasospasm	2.52	1.44–4.44	0.001
Anemia DCI	2.63	1.46–4.76	0.0014
Anemia postprocedure	1.96	1.07–3.59	0.030

CI indicates confidence interval; DCI, delayed cerebral ischemia; GOSE, Glasgow Outcome Scale Extended; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; OR, odds ratio; sBP, systolic blood pressure; and WFNS, World Federation of Neurological Surgeons.

Table 5. Multivariable Logistic Regression of Predictors of Death

	OR	95% CI	*P* Value
Initial sBP	1.01	0.99–1.03	0.144
WFNS	1.84	0.61–5.51	0.27
IVH	1.06	0.85–1.32	0.59
Hijdra	1.07	0.97–1.19	0.17
ICH	0.87	0.26–2.89	0.82
Vasospasm	1.86	1.6–4.81	<0.001
Anemia vasospasm	1.79	0.60–5.35	0.29
Anemia postprocedure	3.50	1.15–10.62	0.027

CI indicates confidence interval; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; OR, odds ratio; and WFNS, World Federation of Neurological Surgeons.

with DIND during vasospasm period: 27.9% [37 of 133] versus 14.5% [34 of 233]; OR, 2.25; 95% CI, 1.29–3.95; *P*=0.0025).

Hemoglobin Thresholds/Receiver Operating Characteristic Curves

To determine precise hemoglobin thresholds associated with poor long-term outcome and death, receiver operating characteristic curves were constructed. The optimal predictive thresholds of hemoglobin postprocedurally associated with poor long-term neurological outcome and death were 9.95 g/dL (sensitivity, 50.9; specificity, 76.8; area under the curve, 0.65) and 9.95 g/dL (sensitivity, 62.5; specificity, 70.7; area under the curve, 0.67), respectively. During the DCI window, optimal predictive thresholds of hemoglobin for poor outcome and death were 9.89 g/dL (sensitivity, 59.4; specificity, 74.2; area under the curve, 0.7) and 9.78 g/dL (sensitivity, 66.7; specificity, 70.1; area under the curve, 0.71), respectively (Figure I in the online-only Data Supplement). Additionally, hemoglobin levels were divided into units of 1 g/dL ranging from <8.0 to >12.1 g/dL postprocedurally and during the DCI window. The rates of unfavorable outcome were significantly higher at hemoglobin levels <10.0 g/dL (postprocedurally and during DCI window: Hb<10.0 g/dL all <0.01; Table II in the online-only Data Supplement; Figure IV in the online-only Data Supplement).

Blood Transfusion, Long-Term Outcome, and Death

Because patients in this study were not randomized to receive blood transfusions, we conducted a propensity matching analysis to balance selected covariates between the transfused and nontransfused cohorts. First, a propensity score matching algorithm matched 35 patients with anemia (<10 g/dL) that were transfused packed red blood cells to 35 patients that were not transfused. In this group of matched patients, there were no differences in outcome or death (unfavorable long-term outcome: anemia without transfusion [48.6%, 17 of 35] versus anemia with transfusion [42.9%, 15 of 35], *P*=0.82; death: anemia without transfusion [8.6%, 3 of 35], versus anemia with transfusion [5.7%, 2 of 35], *P*=0.9).

A second propensity matching algorithm matched 45 patients with Hb >10 g/dL who received a blood transfusion to 45 patients with Hb >10 g/dL who did not receive a transfusion. Interestingly, patients with Hb >10 g/dL who received packed red blood cells had a significantly lower proportion of patients with poor outcomes compared with patients who had Hb levels >10 g/dL and were not transfused (unfavorable neurological outcome: nonanemic with transfusion [2.2%, 1 of 45] versus nonanemic without transfusion [20.0%, 9 of 45]; *P*=0.015), but there were no differences in mortality (mortality: nonanemic with transfusion [0%, 0 of 45] versus nonanemic without transfusion [4.4%, 2 of 45]; *P*=0.49). To determine whether the beneficial effect of blood transfusions occurred within a limited range, additional analyses of patients receiving and not receiving transfusions of blood with a hemoglobin level between 9.01 and 10.0 g/dL or 10.0 and 11.0 g/dL were compared during the DCI window. The DCI window was chosen for this subgroup analysis because of a small sample size of patients who maintained a narrow Hb level between 9.01 and 10.0 g/dL or 10.0 and 11.0 g/dL for the entire duration of the study and that anemia during the DCI window was a stronger predictor of outcome than anemia postprocedurally. There were no significant differences between these groups (9.01–10.0 g/dL transfused [unfavorable outcome: 7 of 14; death: 3 of 14] versus not transfused [unfavorable outcome: 7 of 14; death: 2 of 14]; *P*=0.9 and 0.8, respectively, and 10.01–11 g/dL transfused [unfavorable outcome: 3 of 10; death: 2 of 10] versus not transfused [unfavorable outcome: 3 of 10; death: 3 of 10]; *P*=0.7 and 0.9, respectively).

Discussion

In the present exploratory, post hoc analysis of the CONSCIOUS-1 study,[15] we report several novel findings. First, we demonstrate that low hemoglobin (<10 g/dL) after aSAH occurring after the aneurysm-securing procedure or during the DCI period, but not at the time of hospital admission, is associated with poor neurological outcome and death. Second, we show that variables associated with anemia included a lower presenting neurological grade, aneurysm clipping, female sex, and a higher intraventricular clot burden. Third, transfusion of packed red blood cells (pRBCs) was not associated with improved outcomes in patients who were already anemic, but patients who were transfused to keep their hemoglobins >10 g/dL had better outcomes than those who achieved lower targets—a find that needs to be confirmed in prospective randomized studies.

Decision-making on management of anemia in patients after aSAH is challenging. On one hand, past studies have demonstrated that anemia is an independent risk factor for poor outcome and death after subarachnoid hemorrhage.[10–14,29] Higher hemoglobin concentrations after aSAH have also been reported to be associated with improved outcomes.[13] On the other hand, transfusion has been associated with poor outcomes[13,30,31] and complications, such as infarctions and infections.[10,14] Additionally, beneficial effects of pRBC administration have not been consistently demonstrated.[14,32] The highest quality evidence is derived from a small randomized controlled trial, which did not demonstrate any differences in outcome when patients were randomized to receive transfusion to maintain a hemoglobin level >11.5 versus 10 g/dL, but the study was underpowered to detect potential significant effects.[24]

An unexpected finding from our study was the lack of effect of blood transfusions on anemic patients after aSAH but the positive effect that transfusions conferred to those patients whose hemoglobin was >10 g/dL before a pRBC transfusion.

Previous publications examining the effect of pRBC transfusion after aSAH have all been retrospective studies, except for 1 small prospective randomized controlled trial.[24] Previous retrospective studies were unable to control for the use of pRBCs after aSAH. We are able to expand on previous works by performing propensity score matching analysis, which enabled us to balance covariates between nonrandomized patients. Our findings from this analysis support our initial finding that low hemoglobin is associated with poor outcome and death. Although we demonstrate associations between anemia, poor outcome, death, and DIND in the present study, it remains unknown how to best treat anemia after aSAH. Our data support the maintenance of a liberal transfusion threshold after aSAH, rather than waiting to transfuse as a rescue maneuver at a restrictive threshold, as indicated in other critical care patient populations.[6] An important point to consider is that it remains unknown for how long a period of anemia can be sustained before the detrimental effects cannot be modified.

To further complicate decision-making on the treatment of anemia after aSAH, it remains unknown whether anemia is a surrogate biomarker of disease severity or an independent and modifiable treatment target for patients. After a brain injury, such as aSAH, normal compensatory mechanisms to respond to anemia may be diminished, particularly by arterial vasospasm that could increase cerebral hypoxia. Our data demonstrating that the incidence of DIND is significantly higher in anemic patients after aSAH suggest that these patients are more susceptible to the complications of anemia. Furthermore, several studies using invasive monitoring have shown that hemoglobin <9 g/dL after aSAH has been associated with brain hypoxia[33] and that pRBC transfusions can increase cerebral oxygenation, at least locally,[34] indicating that transfusions of pRBCs may have a beneficial effect, but this remains to be determined in future randomized trials.[35] Interestingly, the hemoglobin level that separates a favorable outcome from an unfavorable outcome has been reported to be as small as 0.5 g/dL,[11,14] suggesting that the differences in hemoglobin thresholds predictive of poor outcome seen in our study and in those by other authors are likely clinically relevant. To add to this, our propensity score analysis data indicate that patients who are already anemic may have crossed a critical threshold for poor outcome and death that cannot be reversed by transfusion. One of the future challenges will be to determine an accurate transfusion threshold for patients after aSAH. Although these data have inherent weaknesses associated with it, it is the highest quality data to date that support a liberal transfusion threshold for patients with aSAH.

The limitations of the current study should be noted. First, the original aim of the CONSCIOUS-1 study was to determine the effect of clazosentan on arterial vasospasm, not the effect of hemoglobin outcome after aSAH. Second, outcome was assessed at 3 months after aSAH, and we do not know whether the effects of anemia persist past this time. Third, the data are a post hoc analysis, and the original study was not designed to determine the effect of blood transfusions on anemia and outcome after aSAH, and the data collected were not able to account for post-transfusion hemoglobin levels in all patients. Furthermore, the presented data are from multiple centers, and the impact of blood products from previously pregnant women, which is associated with an increased risk of acute lung injury,[36] was not controlled for in this study by using a male donor supply. As well, there may be factors that led to patients being transfused with pRBCs that we were unable to account for, such as gastrointestinal hemorrhages, hemodilution, or anemia, because of daily blood work draws. Alternatively, operative complications could have contributed both to anemia and poor outcomes in patients demonstrating low hemoglobin after the aneurysm-securing procedure. We have previously examined operative complications and shown that adverse events in the perioperative period can contribute to unfavorable long-term outcomes,[16] although our preliminary analysis suggested that they do not significantly contribute to anemia. Future work should include a similar analysis of other existing data sets to determine whether the beneficial effect of transfusion >10 g/dL is reproducible and future randomized studies examining the effect of pRBC tranfusions on outcome after aSAH should consider a liberal threshold, as well as the timing of these transfusions.

Conclusions

Anemia after aSAH is an independent risk factor for unfavorable neurological outcome and death. Transfusion of pRBCs after aSAH may have benefit in a select patient population, but this remains to be determined in future studies.

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Actelion Pharmaceuticals, Ltd, was the sponsor of the CONSCIOUS-1 study (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage); the company provided the authors with the study data set but had no role in the analysis or the development of this article. The data analysis and writing are the work of the authors.

Disclosures

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Anemia After Aneurysmal Subarachnoid Hemorrhage Is Associated With Poor Outcome and Death

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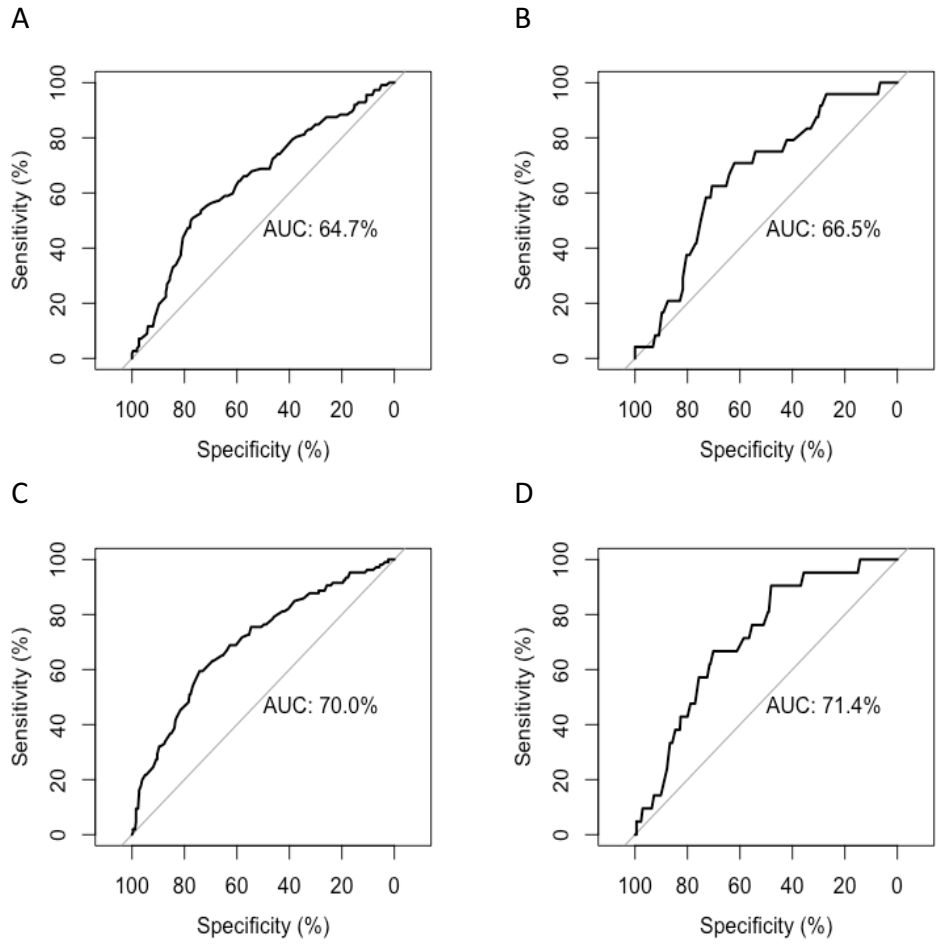
SUPPLEMENTAL MATERIAL

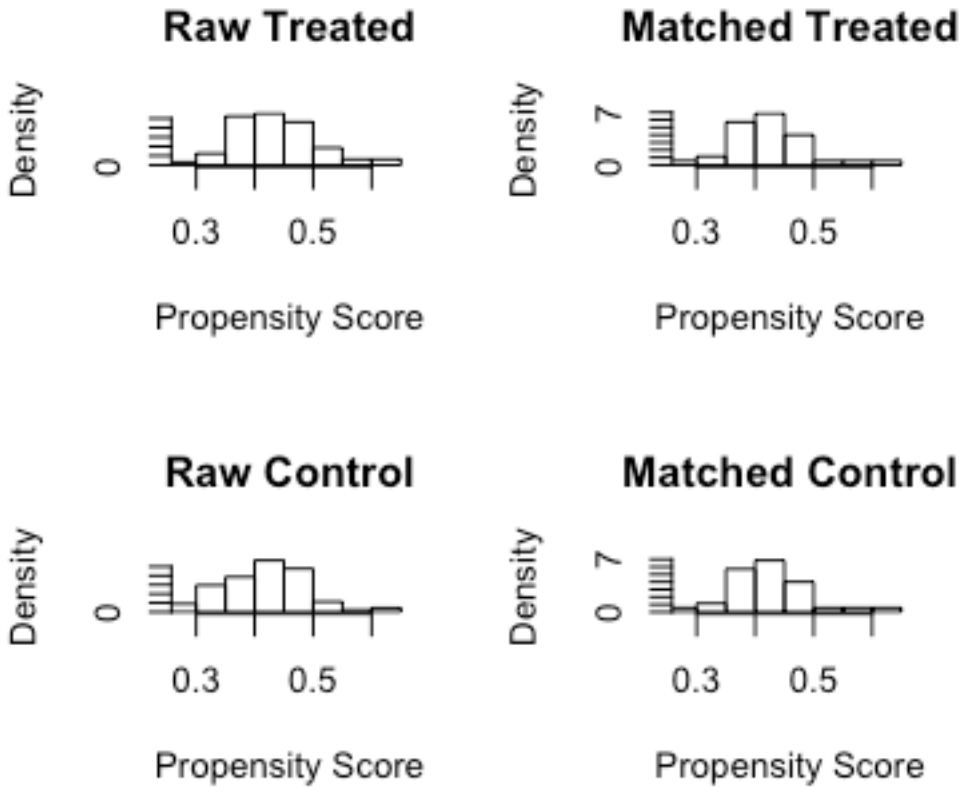
Ayling et al. Anemia after aneurysmal subarachnoid hemorrhage is associated with poor outcome and death

Supplemental Figure I



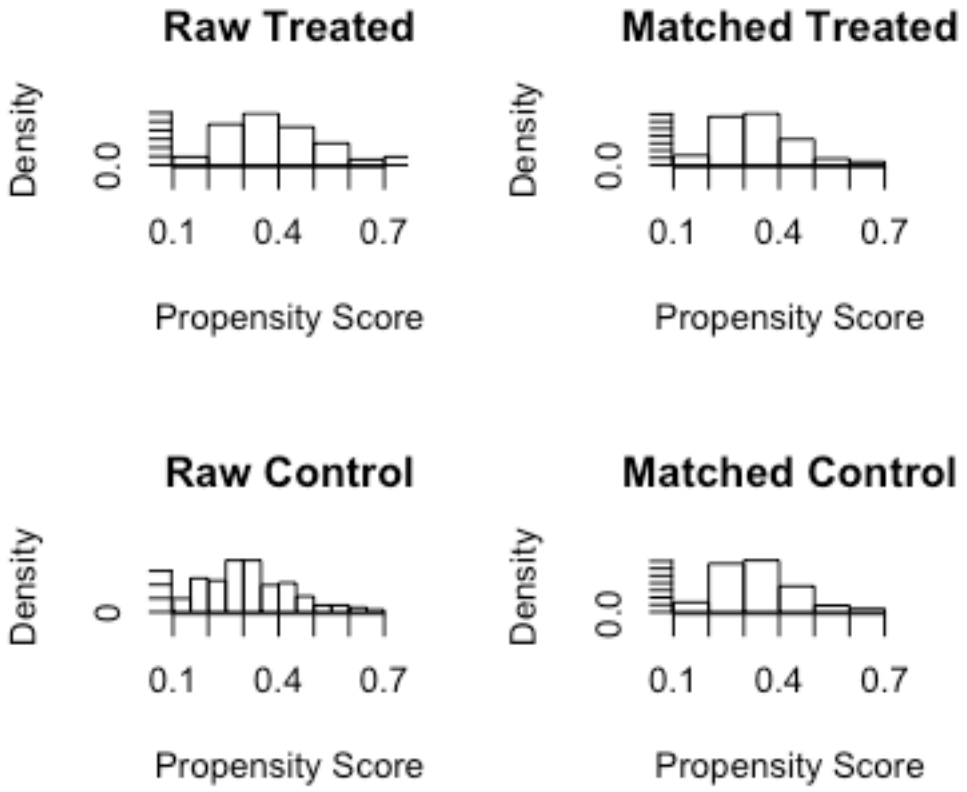
Supplemental Figure I Receiver operator characteristic curves determining the hemoglobin threshold associated with poor outcome and death. Anemia at presentation to hospital was not associated with long-term outcome or death. Post-procedurally, hemoglobin thresholds associated with poor long-term neurological outcome (A) and death (B) were both 9.95 g/dL. During the DCI window predictive thresholds of hemoglobin for poor outcome (C) and death (D) were 9.89 g/dL and 9.78 g/dL, respectively.

Supplemental Figure II



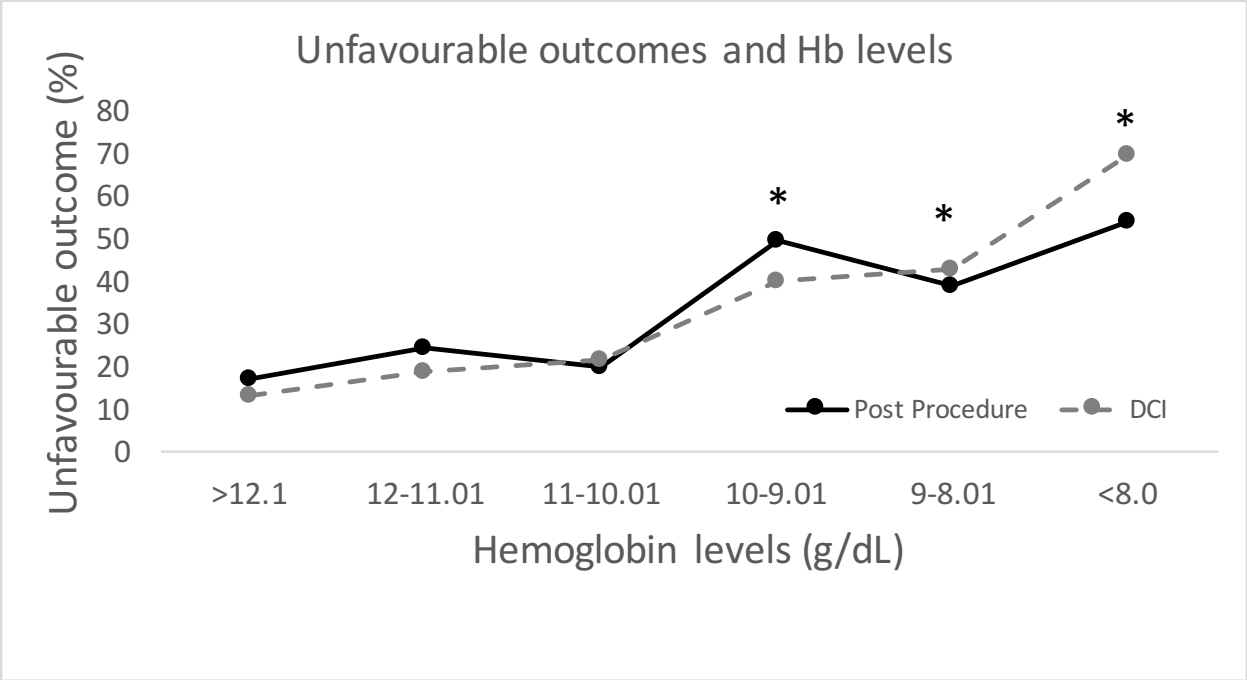
Supplemental Figure II. Histograms of before propensity matching of transfused and anemic patients (raw treated) and anemic but not transfused (raw control). The histograms prior to propensity matching had differing distributions. Histograms after propensity matching (matched treated, and matched control) show similar distributions and suitability of the matching algorithm.

Supplemental Figure III



Supplemental Figure III. Histograms of before propensity matching of transfused patients with Hb >10g/dL (raw treated) and Hb >10g/dL but not transfused (raw control). The histograms prior to propensity matching had differing distributions. Histograms after propensity matching (matched treated, and matched control) show similar distributions and suitability of the matching algorithm.

Supplemental Figure IV



Supplemental Figure IV. Hemoglobin levels and rates of unfavorable outcomes. Black line represents hemoglobin levels and percent of poor outcome on eGOS post-procedurally. The Gray hashed line represented hemoglobin levels and poor outcome rates during the DCI window. Hemoglobin levels below 10g/dL were associated with significantly higher rates of poor outcome post-procedurally and during the DCI window (asterisk = <0.01).

Supplemental Table I
Multivariable logistic regression of surgical complications associated with anemia

	OR	95% CI	p value
burst suppression	0.07	0.09- 1.49	0.62
intra-op aneurysm hemorrhage	0.043	0.012 – 2.34	0.74
intra-op hypotension	0.01	0.01- 1.24	0.97
edema	0.12	0.46- 1.26	0.65
infarction	0.035	0.02- 3.19	0.86
temp clip occlusion	0.014	0.01- 2.23	0.3
induced hypotension	0.058	0.022- 3.27	0.79
intra-op hypertension	0.19	0.1- 1.82	0.42
multiple complications	0.14	0.03- 2.15	0.30

Supplemental Table II
Hemoglobin levels and rates of unfavorable outcomes

	>12.1	**12-11.01**	**-11-10.01**	**10-9.01**	**9-8.01**	**<8.0**
Post-Procedure (N=)	82	87	78	69	44	13
GOSE<5 (N=)	14	21	18	34	17	7
%	17.07	24.14	19.95	49.28	38.64	53.85
p= (vs.>12.1)		0.34	0.43	<0.00001	0.009	0.0072
DCI Window (N=)	75	69	75	70	54	23
GOSE<5 (N=)	10	13	16	28	23	16
%	13.33	18.84	21.33	40.0	42.59	69.57
p= (vs.>12)		0.49	0.28	0.00031	0.00022	<0.00001