Low hemoglobin and hematoma expansion after intracerebral hemorrhage

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Abstract

Objective

Studies have independently shown associations of lower hemoglobin levels with larger admission intracerebral hemorrhage (ICH) volumes and worse outcomes. We investigated whether lower admission hemoglobin levels are associated with more hematoma expansion (HE) after ICH and whether this mediates lower hemoglobin levels' association with worse outcomes.

Methods

Consecutive patients enrolled between 2009 and 2016 to a single-center prospective ICH cohort study with admission hemoglobin and neuroimaging data to calculate HE (>33% or >6 mL) were evaluated. The association of admission hemoglobin levels with HE and poor clinical outcomes using modified Rankin Scale (mRS 4–6) were assessed using separate multivariable logistic regression models. Mediation analysis investigated causal associations among hemoglobin, HE, and outcome.

Results

Of 256 patients with ICH meeting inclusion criteria, 63 (25%) had HE. Lower hemoglobin levels were associated with increased odds of HE (odds ratio [OR] 0.80 per 1.0 g/dL change of hemoglobin; 95% confidence interval [CI] 0.67–0.97) after adjusting for previously identified covariates of HE (admission hematoma volume, antithrombotic medication use, symptom onset to admission CT time) and hemoglobin (age, sex). Lower hemoglobin was also associated with worse 3-month outcomes (OR 0.76 per 1.0 g/dL change of hemoglobin; 95% CI 0.62–0.94) after adjusting for ICH score. Mediation analysis revealed that associations of lower hemoglobin with poor outcomes were mediated by HE ($p = 0.01$).

Conclusions

Further work is required to replicate the associations of lower admission hemoglobin levels with increased odds of HE mediating worse outcomes after ICH. If confirmed, an investigation into whether hemoglobin levels can be a modifiable target of treatment to improve ICH outcomes may be warranted.

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Glossary

APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; **CI** = confidence interval; **GCS** = Glasgow Coma Scale; **HE** = hematoma expansion; **ICH** = intracerebral hemorrhage; **ICU** = intensive care unit; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale; **OR** = odds ratio; **pRBC** = packed red blood cell.

Hematoma expansion (HE) is well known to be associated with worse outcomes after intracerebral hemorrhage (ICH) with the majority of HE occurring within 24 hours of ICH symptom onset.¹ Traditional risk factors for HE include preceding anticoagulant use, faster time from symptom onset to admission CT, and larger baseline hematoma size.² Subsequently, rapid correction of coagulopathy is paramount in treatment paradigms to minimize HE in efforts to improve outcome.³ However, ICH clinical trials to date focused on rapid coagulation factor replacements⁴ and platelet transfusions⁵ to minimize HE have not yielded improved outcomes, suggesting a need to identify additional treatment targets to optimize hemostasis.

The role of erythrocytes and anemia in hemostasis has been described. Specifically, anemia has been associated with increased bleeding events in cardiac patients⁶ with proposed mechanisms being related to lower hemoglobin levels and impaired platelet activation, platelet–platelet interactions, and endothelial binding.⁷ Studies assessing anemia in patients with ICH have shown an association of admission anemia with larger admission hematoma sizes,^{8,9} suggesting coagulopathy related to anemia. Worse outcomes have separately been identified in patients with ICH with lower hemoglobin levels^{8,10} with evidence that packed red blood cell (pRBC) transfusions may be associated with improved 30-day mortality after ICH.¹¹ However, the relationship of low hemoglobin levels and poor outcomes after ICH have been attributed primarily to impaired cerebral oxygen delivery rather than coagulopathy, extrapolating findings seen with anemia in traumatic brain injury and subarachnoid hemorrhage patients.^{12–14}

Liberal pRBC transfusion practices are currently being studied in clinical trial settings for both traumatic brain injury¹⁵ and subarachnoid hemorrhage.¹⁶ However this has yet to be studied in ICH as it is unclear what role lower hemoglobin levels have on ICH and outcome. We sought to test the hypothesis that lower admission hemoglobin levels are associated with increased HE after ICH and that this relationship would mediate the association of lower hemoglobin levels with increased poor outcomes.

Methods

Data were evaluated from an institutional review board–approved, prospective cohort of spontaneous ICH patients consecutively admitted to Columbia University Irving Medical Center. Baseline characteristics, medication history,

neuroimaging, laboratory results, interventions, and outcomes were analyzed for patients enrolled between 2009 and 2016. Patients under 18 years of age were excluded. Patients were managed according to American Heart Association guidelines³ with treatment protocols described previously.¹⁷

Patient selection

Primary patients with ICH with admission hemoglobin laboratory testing along with both baseline and follow-up CT were included. Patients presenting after 24 hours from symptom onset were excluded. Patients with known or suspected secondary ICH (ischemic stroke with hemorrhagic transformation, vascular malformation, aneurysm, malignancy), primary intraventricular hemorrhage (IVH), systemic disease–related coagulopathy as defined by SMASH-U (structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, undetermined) criteria¹⁸ (international normalized ratio >2.0, platelet count <50 × 10³/μL), and those receiving pRBC transfusions or neurosurgery prior to follow-up CT were also excluded (extraventricular drain placement was not excluded) (figure 1). Patients with ICH with anticoagulant medication use were included in order to create a more representative sample of general patients with ICH, whereas systemic disease coagulopathy patients with ICH were excluded as they are known to have significantly worse outcomes due to not only the ICH itself, but the underlying disease process (i.e., cirrhosis).¹⁸

Neuroimaging and outcome assessment

Semi-automatic hematoma size measurements (Medical Imaging Processing, Analysis and Visualization software [MIPAV], NIH) were obtained for all CTs using previously described techniques.^{17,19} Per clinical protocol, patients with ICH received an admission CT and at least one stability CT within 24 hours. Additional scans were obtained based on clinical need. If multiple repeat CT scans were obtained within 24 hours, the latest scan was chosen to measure hematoma size. The interval from symptom onset to admission CT was recorded. HE was calculated as hematoma growth (or size difference) between baseline and stability CT. HE was evaluated primarily as a binary variable using the commonly utilized HE threshold of >33% or >6 mL growth.²⁰ Absolute HE (in mL) from baseline hematoma volume was secondarily assessed as a continuous variable. The primary clinical outcome was poor modified Rankin Scale (mRS 4–6) score at 3-month follow-up. Three-month outcomes were obtained via standardized phone interviews by trained research staff with methodologic details described previously.¹⁷ Secondary clinical outcomes of hospital mortality and discharge poor mRS were additionally assessed.

Figure 1 Patient selection and screening

ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; pRBC = packed red blood cells.

Statistical analysis

Intergroup differences were determined by applying Mann-Whitney *U* or *t* tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. Hemoglobin was assessed as a continuous variable. Pearson bivariate correlation was used to assess correlation of hemoglobin levels and absolute HE defined as a continuous variable. The association of admission hemoglobin levels with HE defined as a binary and continuous variable were separately assessed using adjusted logistic and linear regression models, respectively. Log-transformation was performed for all non-normally distributed data. All HE models were adjusted using previously identified covariates of HE (antithrombotic medication use, baseline hematoma volume, and time to admission CT)² and covariates of hemoglobin (sex and age). Additional multivariable logistic regression models assessed the association of admission hemoglobin level with poor clinical outcomes after adjusting for ICH score (comprising age, baseline ICH size, infratentorial ICH location, presence of IVH, and admission Glasgow Coma Scale [GCS] score).²¹ Additional sensitivity analyses for both HE and clinical outcome models were performed using Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score as a covariate. Mediation analysis was performed to estimate whether HE (as the mediator) was the driving factor for any relationship between hemoglobin level (independent variable) and poor outcome (dependent variable) by regressing all 3 variables together.²² All mediation regressions were linear and all calculations were bootstrapped and estimated at 95% confidence interval (CI) when estimating the coefficients and residuals. Statistical significance was judged at *p* value <0.05. Analyses were performed using SPSS (IBM, Armonk, NY) and MATLAB (MathWorks, Natick, MA).

Standard protocol approvals, registrations, and patient consents

The institutional review board approved this study. Consent was provided by the patient or the family if the patient did not have capacity to consent.

Data availability

All relevant data are presented within the article and its supporting information files. Additional information can be obtained upon request to the corresponding author.

Results

There were 256 patients with ICH meeting inclusion criteria for analysis. Our overall cohort was multiethnic (24% white), had a high prevalence of cardiovascular risk factors, and had a baseline median hematoma size of 13 mL. The admission mean hemoglobin level among all patients with ICH in our cohort was 13.5 g/dL (table 1). There were 21 (8%) patients lost to 3-month follow-up. No HE, hemoglobin, or other laboratory differences were seen between patients included in analysis and those lost to 3-month follow-up.

Intergroup differences between patients with ICH who encountered HE and those without are shown in table 1. There were no baseline demographic differences, but there were worse baseline clinical severity scores (GCS and ICH score), higher antithrombotic medication use (both anticoagulant and antiplatelet use), and faster times from symptom onset to admission CT in those with HE. There were no significant

Table 1 Baseline intracerebral hemorrhage (ICH) characteristics: Differences between patients with ICH with and without hematoma expansion (HE)

	All ICH (n = 256)	HE (n = 63)	No HE (n = 193)	p Value
Age, y, mean (SD)	66 (15)	68 (17)	66 (15)	0.29
Female, n (%)	115 (45)	26 (41)	89 (46)	0.56
Race, n (%)				
White	62 (24)	19 (30)	43 (22)	0.17
Black	75 (29)	17 (27)	58 (30)	
Hispanic	104 (41)	21 (33)	83 (43)	
Other/unknown	15 (6)	6 (10)	9 (5)	
Medical history, n (%)				
Dyslipidemia	67 (26)	19 (30)	48 (25)	0.41
Coronary artery disease	38 (15)	14 (22)	24 (12)	0.07
Atrial fibrillation	31 (12)	13 (21)	18 (9)	0.03
Hypertension	211 (82)	48 (76)	163 (85)	0.18
Diabetes	79 (31)	24 (38)	55 (29)	0.16
Medication history, n (%)				
Antiplatelet	101 (40)	33 (52)	68 (35)	0.02
Anticoagulation	38 (15)	17 (27)	21 (11)	0.004
Statin	53 (21)	16 (25)	37 (19)	0.29
Clinical/radiographic				
GCS, median (IQR)	11 (7–15)	8 (4–14)	12 (8–15)	<0.001
ICH score, median (IQR)	2 (1–3)	2 (1–3)	1 (1–2)	0.001
APACHE score, mean (SD) ^a	15 (8)	18 (8)	14 (7)	0.001
ICH volume, mL, median (IQR)	13 (4–32)	19 (6–35)	11 (4–30)	0.14
Deep location, n (%)	163 (64)	43 (68)	120 (62)	0.45
Lobar location, n (%)	67 (26)	17 (27)	51 (26)	1.00
Brainstem location, n (%)	11 (4)	0 (0)	11 (6)	0.07
Infratentorial location, n (%)	14 (6)	3 (5)	11 (6)	1.00
IVH, n (%)	124 (50)	30 (51)	94 (50)	1.00
Symptom onset to baseline CT, h, median (IQR)	5.6 (1.6–11.0)	3.5 (1.1–6.8)	6.9 (2.1–11.8)	0.001
Time between CTs, h, median (IQR)	9.8 (6.2–15.4)	8.7 (5.5–12.9)	9.9 (6.3–15.9)	0.19
Admission SBP, mm Hg, mean (SD)	188 (38)	189 (34)	188 (39)	0.91
Admission DBP, mm Hg, mean (SD)	102 (25)	99 (21)	102 (26)	0.49
Absolute HE, mL, median (IQR)	0.2 (–0.7 to 3.1)	10.5 (5.5–21.6)	–0.2 (–1.1 to 0.6)	<0.001
Laboratory coagulation testing, mean (SD)				
PT, s	15.3 (6.1)	17.1 (6.9)	14.7 (5.8)	0.01
PTT, s	30.2 (6.6)	31.8 (8.6)	29.7 (5.8)	0.05
INR	1.3 (0.7)	1.4 (0.7)	1.2 (0.6)	0.05
Platelet count, 10 ³ /μL	226 (65)	215 (76)	229 (60)	0.14

Continued

Table 1 Baseline intracerebral hemorrhage (ICH) characteristics: Differences between patients with ICH with and without hematoma expansion (HE) (continued)

	All ICH (n = 256)	HE (n = 63)	No HE (n = 193)	p Value
Blood count				
Hemoglobin, g/dL, mean (SD)	13.5 (1.8)	12.9 (1.9)	13.7 (1.7)	0.01
Hematocrit, n (%)	40.4 (4.9)	39.3 (5.3)	40.7 (4.7)	0.04
Outcome, n (%)				
Discharge death	47 (19)	22 (36)	25 (13)	<0.001
Discharge poor mRS (4–6)	205 (81)	56 (92)	149 (77)	0.01
3-month poor mRS (4–6) ^b	163 (69)	48 (80)	115 (66)	0.05

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; INR = international normalized ratio; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; PT = prothrombin time; PTT = partial thromboplastin time; SBP = systolic blood pressure.

^a APACHE II scores missing for 5% (n = 12); percentages from 244 patients: 56 with HE, 188 without HE.

^b 3-month loss to follow-up was 8% (n = 21); percentages from 235 patients: 50 with HE, 175 without HE.

differences in baseline hematoma volumes or admission systolic blood pressures between groups. Patients with HE had lower admission hemoglobin (mean 12.9 g/dL vs 13.7 g/dL) and hematocrit (mean 39.3% vs 40.7%).

Multivariable logistic regression models revealed that lower hemoglobin levels were associated with increased odds of HE (adjusted odds ratio [OR] of HE per 1.0 g/dL change in hemoglobin 0.80; 95% CI 0.67–0.97; $p = 0.02$) (table 2). When evaluating HE as a continuous variable of absolute growth (in mL), lower hemoglobin was inversely correlated with increased absolute HE ($R = -0.13$; $p = 0.04$). Multivariable linear regression was additionally assessed to evaluate the association of hemoglobin to HE as a continuous variable of hematoma growth (in mL). There was an association of lower hemoglobin levels with increased absolute HE growth (B-coeff -0.67 ; 95% CI -1.36 to 0.03 ; $p = 0.06$) after adjusting for the same covariates, but this estimate was imprecise. We did not identify a correlation between lower admission hemoglobin levels and larger baseline hematoma volumes ($R = -0.02$; $p = 0.81$).

Given the inherent possibility that patients with lower hemoglobin levels were sicker patients on admission, APACHE

II scores were additionally explored. Mean APACHE II scores were worse in those with HE compared to those without (table 1). There was no evidence of collinearity between APACHE II scores and hemoglobin. There continued to be an association of lower hemoglobin to increased odds of HE in sensitivity analyses including APACHE II score as a covariate (adjusted OR of HE per 1.0 g/dL change in hemoglobin 0.82; 95% CI 0.67–0.99; $p = 0.04$).

When evaluating relationships between admission hemoglobin levels and 3-month outcomes, we identified an association of lower hemoglobin levels with increased odds of poor 3-month outcomes (adjusted OR of poor outcome per 1.0 g/dL change in hemoglobin 0.76; 95% CI 0.62–0.94; $p = 0.01$) after adjusting for ICH score. Additional analyses adjusting for sex or APACHE II did not change the findings. Lower hemoglobin levels were not associated with increased hospital mortality or discharge poor mRS (table 2).

When regressing hemoglobin, HE, and outcome together, mediation analysis revealed that increasing HE continued to be associated with poor outcome after controlling for hemoglobin level ($p = 0.01$, significance revealed in 95% CI).

Table 2 Crude and adjusted logistic regression assessing association of hemoglobin levels with hematoma expansion (HE) and neurologic outcomes

Hemoglobin	HE >33% or >6 mL, ^a OR (95% CI); p value	Hospital mortality, ^b OR (95% CI); p value	Discharge mRS 4–6, ^b OR (95% CI); p value	3 months mRS 4–6, ^{b,c} OR (95% CI); p value
Crude	0.80 (0.68–0.95); $p = 0.01$	0.96 (0.80–1.14); $p = 0.62$	0.98 (0.82–1.16); $p = 0.79$	0.80 (0.68–0.94); $p = 0.01$
Adjusted	0.80; (0.67–0.97); $p = 0.02$	0.97 (0.80–1.17); $p = 0.77$	1.06 (0.85–1.32); $p = 0.62$	0.76 (0.62–0.94); $p = 0.01$

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; OR = odds ratio.

OR interpreted as odds of outcome (HE or poor mRS) for every 1.0 g/dL change in hemoglobin (OR less than 1.00 indicates lower hemoglobin levels with higher odds of outcome).

^a Model adjusted for antithrombotic medication history, time from symptom onset to admission CT, admission intracerebral hemorrhage volume, age, sex.

^b Model adjusted for intracerebral hemorrhage score.

^c 3-month loss to follow-up was 8% (n = 21).

This suggested that HE significantly mediated the effect of lower hemoglobin levels with poor 3-month outcomes (figure 2). Efforts to identify appropriate hemoglobin thresholds associated with clinical outcomes were limited secondary to limited numbers of patients with ICH with lower hemoglobin levels. While exploratory analyses using previously utilized categorization of hemoglobin levels (hemoglobin >13, 11–13, 9–11, and <9 g/dL)⁹ appeared to reveal more HE and worse 3-month outcomes at admission hemoglobin levels below 11 g/dL (figure 3, A and B), we were unable to appropriately assess this given the limited patients in the 9–11 g/dL and <9 g/dL hemoglobin categories.

Discussion

In our primary ICH cohort, we were able to identify that lower admission hemoglobin levels were associated with increased odds of HE. Consistent with prior studies,^{8,10} we were additionally able to identify an association of lower admission hemoglobin levels with worse outcomes. This relationship seemed to be mediated in part by HE.

Unlike prior studies, we were unable to identify an inverse relationship between lower hemoglobin levels and larger baseline ICH volumes.^{8,9,11} Though preceding antithrombotic medication use was similar to previously reported ICH cohorts studying hemoglobin, our cohort's overall baseline hematoma sizes were smaller.^{9,11} These differences may have been explained by the exclusion of patients with ICH with delayed presentation times in our cohort, thus creating an ICH cohort that had not yet encountered HE resulting in smaller admission hematoma volumes. Prior studies did not exclude patients with delayed presentation times and additionally did not include information on times from symptom onset to admission CT, a well-known predictor of HE. It is possible that these prior

studies conversely comprised a more delayed symptom onset cohort that already encountered HE, creating the larger baseline hematoma sizes that were seen. However, it is also possible that these differences may be a reflection of our specific patient cohort, as seen with our racially diverse patient population, higher prevalence of cardiovascular risk factors, and higher prevalence of deep ICH location compared to other studies.

It is plausible that the pathophysiologic basis for our findings of more HE in patients with lower hemoglobin levels may be related to previously shown evidence of coagulopathy and prolonged bleeding in anemic patients.⁷ Lower erythrocyte counts may result in less efficient radial transport of platelets toward the vessel wall, preventing the platelet endothelial interaction vital to hemostasis initiation. In addition, erythrocytes themselves may be implicated in hemostasis through their adhesion to the injured vessel wall in addition to their interaction with platelets and fibrinogen leading to blood clot contraction.²³

Trends in current pRBC transfusion practices utilize restrictive transfusion thresholds of <7.0 g/dL²⁴ given risks associated with pRBC transfusions²⁵ and noninferiority in restrictive pRBC transfusion approaches in non-neurologic intensive care unit (ICU) patients.²⁶ This practice is often carried over to neurologic ICU patients; however, it is unclear if these guidelines are translatable to patients with acute brain injury. In our cohort, HE and poor outcomes appeared to occur at hemoglobin levels higher than these restrictive thresholds (7.0 g/dL). However, attempts to accurately identify optimal hemoglobin thresholds associated with outcome were limited secondary to our smaller cohort sample.

The concept of liberal pRBC transfusion approaches in patients with acute brain injury is actively being studied, specifically in patients with traumatic brain injury²⁵ and subarachnoid hemorrhage.²⁶ However, liberal pRBC transfusion has yet to be studied in ICH as it is still unclear whether treating low hemoglobin levels will improve outcome. Though prior studies have suggested that pRBC transfusions may improve mortality after ICH,¹¹ it is feasible that our findings may reflect that lower admission hemoglobin levels are a surrogate marker of poor outcome rather than a modifiable risk factor that can be targeted to improve outcomes. Given the observational construct of the study, it is difficult to elucidate whether the associations of lower hemoglobin to more HE and worse outcomes is simply a reflection of patients with lower hemoglobin levels being sicker patients with more comorbidities on admission. However, we included models adjusting for APACHE II score to attempt to account for this and did not note a change in hemoglobin's association with HE or neurologic outcome.

While prior ICH studies have suggested pRBC transfusions may improve outcome by optimizing cerebral oxygen delivery, this presumptive mechanism has been extrapolated from findings seen in traumatic brain injury and subarachnoid hemorrhage. There are no multimodality monitoring or brain tissue oxygenation data yet to support this in patients with

Figure 2 Mediation analysis of association of lower hemoglobin levels with poor neurologic outcome with hematoma expansion as a mediator

Lower hemoglobin levels were independently associated with more hematoma expansion (gray arrow; $p = 0.003$) and worse neurologic outcomes (gray arrow; $p = 0.03$). Hematoma expansion was associated with poor outcome while controlling for hemoglobin levels (black arrow; $p = 0.01$), suggesting that hematoma expansion mediates the relationship between low hemoglobin levels and poor outcome.

Figure 3 Hematoma expansion and outcome among different admission hemoglobin concentrations

ICH. If hemoglobin is in fact a modifiable target of treatment to improve outcome, this mechanism raises the question of the timing of liberal pRBC transfusion approaches in ICH. Our data may suggest hyperacute transfusion of pRBC can be considered in preventing the early occurrence of HE to improve outcome; however, replication of our findings in addition to clarifying whether lower hemoglobin levels also have a negative effect on ICH outcomes independent of HE are required. Further work is required to identify biological/mechanistic underpinnings for the associations identified in our study along with appropriate hemoglobin thresholds associated with neurologic outcomes and HE. In addition, risks of pRBC transfusions in patients with ICH and optimal temporality of pRBC transfusions need to be identified prior to considering interventions using pRBC approaches.

Our study strengths include the prospective collection of data, the multidisciplinary consensus adjudication of ICH

characteristics, and the relative protocolization of ICH treatment at our center limiting treatment and diagnostic scanning heterogeneity. Inherent limitations of our study included its single-center design, loss to follow-up, absence of CT angiography spot sign testing, and limited patients who received pRBC transfusions prior to stability CT preventing an analysis on the effect of hyperacute pRBC transfusion on HE and outcome. In addition, though the large exclusion group may be a limitation, this was necessary to appropriately evaluate HE and mirrored exclusion criteria seen in ICH clinical trials. Finally, our smaller numbers prevented adequately identifying a hemoglobin threshold that could be utilized to minimize HE.

Further investigation is warranted to confirm our findings of more HE after ICH in patients with lower admission hemoglobin levels resulting in worse clinical outcomes. If confirmed, these findings may suggest the importance of accounting for

and correcting hemoglobin levels in future ICH coagulopathy treatment strategies for HE in efforts to improve outcome.

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Disclosure

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Appendix (continued)

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