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ORIGINAL ARTICLE

Red Blood Cell Transfusion Increases the Risk of Thrombotic Events in Patients with Subarachnoid Hemorrhage

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Abstract
Background and Purpose Red blood cell transfusion (RBCT) may increase the risk of thrombotic events (TE) in patients with subarachnoid hemorrhage (SAH) through changes induced by storage coupled with SAH-related hypercoagulability. We sought to investigate the association between RBCT and the risk of TE in patients with SAH.
Methods 205 consecutive patients with acute, aneurysmal SAH admitted to the neurovascular intensive care unit of a tertiary care, academic medical center between 3/2008 and 7/2009 were enrolled in a retrospective, observational cohort study. TE were defined as the composite of venous thromboembolism (VTE), myocardial infarction (MI), and cerebral infarction noted on brain CT scan. Secondary endpoints included the risk of VTE, poor outcome (modified Rankin score 3–6 at discharge), and in-hospital mortality.
Results 86/205 (42 %) received RBCT. Eighty-eight (43 %) had a thrombotic complication. Forty (34 %) of 119 non-transfused and 48/86 (56 %) transfused patients had a TE ($p = 0.002$). In multivariate analysis, RBCT was associated with more TE by [OR 2.4; 95 % CI (1.2, 4.6); $p = 0.01$], VTE [OR 2.3; 95 % CI (1.0, 5.2); $p = 0.04$], and poor outcome [OR 5.0; 95 % CI (1.9, 12.8); $p < 0.01$]. The risk of TE increased by 55 % per unit transfused when controlling for univariate variables. Neither mean nor maximum age of blood was significantly associated with thrombotic risk.
Conclusions RBCT is associated with an increased risk of TE and VTE in SAH patients. A dose-dependent relationship exists between number of units transfused and thrombosis. Age of blood does not appear to play a role.

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Introduction

Red blood cell transfusions (RBCT) are often administered to patients with subarachnoid hemorrhage (SAH) to augment cerebral perfusion, to decrease cerebral hypoxia, and to minimize cerebral ischemia. However, although hemoglobin concentration can be augmented by the administration of red blood cells (RBCs), transfusions do not consistently increase tissue oxygen utilization, especially in critically ill patients [1, 2]. Furthermore, RBCT are not benign; they have been associated with an increased risk of nosocomial infection, ventilator-associated pneumonia, and acute lung injury [3–5].

Blood storage results in biochemical and physical changes that impede RBC function [6–8]. Depletion of 2,3-diphosphoglycerate acid (2,3 DPG) and adenosine triphosphate (ATP) alters RBC morphology and deformability which decreases the ability of RBCs to off-load oxygen and traverse capillaries [9, 10]. RBC storage accelerates the release of free hemoglobin, which reduces nitric oxide concentrations, causing subsequent vasoconstriction [11]. The binding and inactivation of nitric oxide may also lead to intravascular thrombosis mediated by white blood cell adhesion, endothelial permeability, and smooth muscle proliferation after vascular injury [12].

Abnormal coagulation and fibrinolysis have been reported in SAH patients [13, 14]. Elevations in coagulation and fibrinolytic parameters correlate with poor clinical outcome [13–15]. The relative hypercoagulable state observed in SAH patients may be related to intimal damage of the cerebral vessels, release of thromboplastin from the injured brain, elevated levels of biogenic amines from the hemorrhage, or dissolved clot in the subarachnoid space entering the circulation [13].

Given the physical and biochemical changes induced by RBC storage coupled with alterations in coagulation and fibrinolysis in SAH patients, we hypothesized that RBCT is associated with an increased risk of thrombosis in SAH patients.

Methods

Study subjects consisted of consecutive patients between March 2008 and July 2009 admitted with SAH to the Jefferson Hospital for Neuroscience, a tertiary care academic hospital that treats over 400 cerebral aneurysms annually. Patients were identified from a prospectively collected database. A retrospective review was performed after obtaining approval from the Institutional Review Board. The diagnosis of aneurysmal SAH was established on the basis of computed tomographic (CT) scan or, if the CT was non-diagnostic, by xanthochromia of the cerebrospinal fluid (CSF). Patients with SAH from antecedent head trauma, ischemic or hemorrhagic stroke, vascular malformation, or other secondary causes were excluded as were patients with angionegative or perimesencephalic SAH. Patients who were not admitted within three days of ictus or did not survive to hospital day three were excluded.

Demographic data, including age, sex, and race, as well as clinical and laboratory data were recorded. Hunt and Hess classifications were determined by the admitting resident physician and based on the clinical examination obtained in the Emergency Department. Fisher group was recorded on the basis of the initial head CT and adjudicated by a neurointensivist (MM). Aneurysm size and location were recorded based on information from catheter angiography or operative reports. Recorded laboratory parameters included baseline serum hemoglobin concentration (g/dL), white blood cell (WBC) count (number/mL), platelet count (thousand/mL), coagulation profile, and serum creatinine.

All patients were treated according to a standard protocol. Patients experiencing symptomatic cerebral ischemia received hypertensive euvolemic therapy. Transcranial Doppler ultrasound studies were performed twice daily from admission to hospital day 21 for all patients with adequate temporal bone windows. Mean velocities of >200 cm/s in the middle cerebral arteries and Lindegaard ratios of >3 were recorded as evidence of TCD vasospasm. Intracranial hypertension was treated according to a step-wise protocol. Blood transfusions were administered according to local clinical protocol to maintain hemoglobin ≥ 10 g/dL.

Lower extremity sequential compression devices (SCDs) were placed on all patients upon admission except if an acute DVT was known or suspected. Thromboprophylaxis with daily administration of subcutaneous enoxaparin (40 mg) was initiated on day 2 of hospitalization or on the morning after aneurysm treatment. Surveillance Doppler ultrasounds for lower extremity DVT were performed twice weekly on all patients. Upper extremity ultrasounds were performed when there was a suspicion of thrombosis.

The primary endpoint was the development of TE, defined a priori as the composite of any deep venous thrombosis (DVT), pulmonary embolism (PE), cerebral infarction, myocardial infarction (MI), bowel ischemia, adrenal thrombosis, retinal ischemia, or peripheral embolism; however, no cases of bowel ischemia, adrenal thrombosis, retinal ischemia, or peripheral embolism were identified. MI was defined as troponin elevation with ECG changes and regional wall motion abnormalities not attributed to stress cardiomyopathy. Ischemic changes that were reversible, as determined by follow up echocardiography, were not classified as acute myocardial infarction. Cerebral

infarction was defined as any infarction, not present on admission, noted on either the last obtained head CT or head CT obtained closest to post-hemorrhage day 21. Secondary endpoints included the risk of venous thromboembolism (VTE), poor outcome defined as a modified Rankin score (mRS) 3–6 at hospital discharge, and in-hospital mortality. VTE was defined as the subset of TE comprised solely of DVT and PE. Transfusions performed after the detection of the primary endpoint were not included in the analysis; only transfusions occurring before the primary endpoint were included. Clinical outcomes were assessed by in-hospital mortality rates and modified Rankin score at discharge.

Blood product transfusion records were obtained from the electronic database maintained by the Transfusion Medicine Department. Nearly all units (>95 %) were leukoreduced pre-storage. Blood component type, ABO antibody type, Rh factor type, unit number, transfusion date, expiration date, and product code were recorded. The additive solution was also noted, as the shelf life of RBCs depends on the type of additive solution used. A 35-day shelf life was assumed for citrate–phosphate-dextrose-adenine (CPDA) blood. A 42-day shelf life was assumed for all non-CPDA blood [predominantly AS-3 (sodium chloride-phosphate-adenine-glucose)], although some other additive solutions may have been used for imported units. The age of blood was calculated using the date of expiration, the shelf life, and the date of administration. For patients receiving more than one unit of RBCs, the mean, median, and maximum age of blood per patient were calculated and analyzed.

Continuous variables are reported as mean (standard deviation). Univariate analyses of continuous variables were analyzed using the students *t* test, while univariate analysis of non-normally distributed data were performed using the Wilcoxon rank sum test and Spearman rank-correlation coefficient. Categorical variables were compared using Chi squared test for significance. Multivariable analyses using logistic regression to identify predictors of thrombosis included all variables associated with thrombosis in univariate analysis ($p < 0.1$). Due to collinearity, Hunt and Hess grade, and not Fisher group, was used in the regression models as the measure of initial disease severity. Multivariable logistic regression was also performed to identify predictors of VTE, mortality, and poor outcome. Secondary analyses including length of stay were performed for all outcome variables (TE, VTE, and poor outcome). Attributable risk was determined for RBC transfusion and other known determinants of TE independent of univariate predictors. All data were analyzed using STATA/SE 10.0 software (College Station, TX).

Results

The clinical characteristics of the study cohort are displayed in Table 1. Of the 205 patients included in the study, 86 (42 %) were transfused. Eighty-eight patients (43 %) experienced a thrombotic event. Fifty-four patients experienced cerebral infarction, 18 had VTE, 13 had both infarction and VTE, 2 had VTE and MI, and one had an MI alone. More patients in the transfused group had TE than in the non-transfused group [48/86, (56 %) versus 40/119 (28 %), $p = 0.002$] in univariate analysis (Table 2). The incidence of VTE was also significantly higher in the transfused group (21/86 (24 %) versus 12/119 (9 %), $p = 0.007$). Thirty-seven of 86 (43 %) of transfused patients experienced a cerebral infarction compared to 30/119 (25 %) of non-transfused patients ($p = 0.01$).

RBC transfusion was independently associated with TE in multivariate analysis (Table 3). This effect was independent of age, sex, Hunt and Hess grade, admission hemoglobin concentration, surgical intervention, arterial

Table 1 Demographic characteristics of entire cohort

	Transfused $n = 86$ (%)	Not transfused $n = 119$ (%)	p	n
Age, years, mean (SD)	57.1 (14.2)	55.6 (13.6)	0.46	
Women	67 (78)	75 (63)	**0.03**	
White	47 (55)	75 (63)	0.25	
Hypertension	69 (80)	98 (82)	0.72	
Diabetes mellitus	25 (29)	28 (24)	0.42	
Coronary artery disease	8 (9)	15 (13)	0.51	
Tobacco use (ever)	42 (48)	62 (52)	0.67	
Anterior aneurysm location	71 (83)	102 (86)	0.56	
Multiple aneurysms	11 (13)	14 (12)	0.83	
Aneurysm treatment				
Endovascular	58 (67)	102 (86)	**<0.01**	
Surgical	25 (29)	12 (10)	**<0.01**	
Any intervention	86 (100)	114 (96)	0.08	
Hunt and Hess grade				
1–3	55 (64)	104 (87)	**<0.01**	
4–5	31 (36)	15 (13)		
Fisher Group				
3	70 (81)	88 (74)	0.24	
1, 2 or 4	16 (19)	31 (26)		
TCD vasospasm	24 (28)	18 (15)	**0.04**	
Mean admission hemoglobin, g/dL (SD)	12.3 (1.9)	13.7 (1.6)	**<0.01**	
Hospital day of initiation of VTE pharmacoprophylaxis, median (IQR)	4.0 (3–5)	3.6 (2–4)	0.07	
Thrombotic events (TE)				
Cerebral infarction				67
DVT				27
PE				10
MI				3

Values in boldface indicate significance at the <0.05 level

Table 2 Univariate predictors of thrombotic events (TE)

	Thrombotic event $n = 88$ (%)	No thrombotic event $n = 117$ (%)	p
Mean age, years (SD)	57.6 (15.1)	55.2 (12.8)	0.22
Women	63 (72)	79 (68)	0.55
White	51 (58)	71 (61)	0.77
Hypertension	68 (77)	99 (85)	0.21
Diabetes mellitus	24 (27)	29 (25)	0.75
Coronary artery disease	11 (13)	12 (10)	0.66
Tobacco use (ever)	43 (49)	61 (52)	0.67
Anterior aneurysm location	71 (81)	102 (87)	0.25
Surgical treatment of aneurysm	18 (20)	19 (16)	0.47
Hunt and Hess grade 4–5	28 (32)	18 (15)	**0.007**
Fisher group 3	77 (88)	81 (69)	**0.002**
TCD vasospasm	23 (26)	19 (16)	0.12
RBC transfusion	48 (55)	38 (32)	**0.002**
Mean admission hemoglobin, g/dL (SD)	13.0 (2.1)	13.2 (1.7)	0.50
Mean RBC age, days (SD)	22.3 (7.7)	24.4 (7.5)	0.22
FFP transfusion	14 (16)	10 (9)	0.12

Values in boldface indicate significance at the <0.05 level

Table 3 Multivariate logistic regression associated with thrombotic events (TE)

	OR	95 % CI	p
RBC transfusion	2.4	(1.2, 4.6)	**0.01**
Age	1.0	(1.0, 1.0)	0.19
Male sex	0.9	(0.5, 1.8)	0.74
Hunt and Hess grade 4–5	1.9	(0.9, 4.0)	0.09
Admission hemoglobin	1.1	(0.9, 1.3)	0.35

Value in boldface indicate significance at the <0.05 level

vasospasm, and FFP use. Transfusion increased the odds of TE by 2.1 [95 % CI (1.1, 4.2) $p = 0.03$] and VTE by 2.4 [95 % CI (1.0, 5.4) $p = 0.04$] in multivariate analysis. There was a dose-dependent effect of transfusion; the risk of TE increased by 55 % per unit transfused when controlling for univariate predictors [95 % CI (1.3, 1.9) $p < 0.001$]. Correcting for length of stay in multivariable analysis did not attenuate the association between transfusion and TE [OR = 2.1, 95 % CI (1.1, 3.8) $p = 0.02$] or VTE [OR = 2.5 [95 % CI (1.1, 5.7) $p = 0.03$].

Eighty-six patients were transfused a total of 388 units of RBCs. Surgical intervention, high Hunt and Hess grade, and admission hemoglobin were significantly associated with transfusion. Female sex and age were not associated with transfusion. Median hospital day of transfusion was 4.5 days (IQR 3–8). The majority of blood was type O positive (60.8 %). The mean age of transfused blood was 22.4 ± 7.6 days, with a minimum of 3 days and a maximum of 42 days. Neither mean nor maximum age of blood was associated with TE. Analysis of age of blood failed to demonstrate an association with TE.

Table 4 Multivariate logistic regression associated with poor outcome (mRS 3–6)

	OR	95 % CI	p
RBC transfusion	5.0	(1.9, 12.8)	**0.001**
Age	1.1	(1.0, 1.1)	**<0.001**
Hunt and Hess grade 4–5	9.1	(2.4, 34.5)	**0.001**
Admission hemoglobin	1.3	(1.0, 1.7)	**0.03**
Arterial vasospasm	4.9	(1.7, 13.8)	**0.003**
Male sex	0.7	(0.3, 1.7)	0.48
Surgical intervention	1.1	(0.4, 3.1)	0.81
Thrombotic event	2.0	(0.9, 4.4)	0.09
FFP transfusion	1.1	(0.3, 4.5)	0.84

Values in boldface indicate significance at the <0.05 level

Poor outcome, defined by a modified Rankin score of 3–6, occurred in 122 (60 %) patients, including 18 deaths (9 %). Red blood cell transfusion increased the odds of poor outcome five-fold, independent of age, sex, Hunt and Hess class, admission hemoglobin, arterial vasospasm, surgical intervention, FFP administration, and thrombotic event (Table 4). Each unit of transfused blood conferred an 81 % increase in the adjusted odds of poor outcome [95 % CI (1.3, 2.5) $p < 0.001$. In univariate analysis, transfusion increased the odds of death by 5.6 [$p = 0.003$ (1.8, 17.6)]; however, the low mortality rate precluded multivariate analysis.

Discussion

Our data suggest that RBCT is associated with an increased risk of TE in SAH patients. This relationship was independent of age, sex, injury severity, and admission hemoglobin. Secondary analysis, including length of stay, did not change the significance or magnitude of the effect. There was a dose-dependent effect of transfusion; the risk of TE increased by over 50 % per unit transfused when controlling for univariate associations. Accounting for these associations, the attributable risk of transfusion on thrombosis was 22.0 %, which was greater than the effect of Fisher group, a widely accepted predictor of DCI and stroke after SAH, on cerebral infarction (17.8 %).

Studies in non-SAH patients corroborate the association between RBCT and thrombotic complications [16–18]. RBCT was identified as an independent risk factor for the development of DVT in a two studies of trauma patients [17, 18]. In a nationwide database study of over 500,000 cancer patients, RBCT was significantly and independently

associated with the development of VTE with an odds ratio of 1.6 [95 % CI (1.53, 1.67) $p < 0.001$) [16]. Arterial TE were also more prevalent among patients who were transfused [5.2 vs 3.0 % ($p < 0.001$)] [16].

SAH patients may be prone to a transient hypercoagulable state mediated by tissue factor release and catalyzed by the inflammatory cascade. The brain has the body's highest concentrations of tissue factor, much of it localized in the adventitia of cerebral arteries and perivascular astrocytes [19]. Stein and colleagues proposed that after aneurysm rupture, exposure of the adventitial surface of cerebral vessels to subarachnoid blood may incite local disseminated intravascular coagulation (DIC) [20]. Subarachnoid blood also activates endothelial cells of larger vessels, creating a local hypercoagulable milieu which may further contribute to a transient hypercoagulable state [21].

The presence of coagulopathy after SAH is supported by numerous studies demonstrating activation of both the coagulation and fibrinolytic systems in peripheral blood samples of SAH patients [22–24]. Activation of the coagulation system manifests as increased plasma thrombin-antithrombin (TAT) complexes, whereas activation of the fibrinolytic system is characterized by a documented increase in plasma D-dimer levels [13, 15, 29]. Both TAT and D-dimer levels have been shown to correlate with severity of illness in SAH patients [13, 15, 24].

Other possible mechanisms may explain the association between transfusion and thrombosis. RBCT augments blood viscosity which results in turbulent flow and increased platelet interactions, putatively culminating in thrombosis [25]. Furthermore, endothelial NO causes vasodilatation, increased blood flow, reduced blood pressure, and inhibition of platelet adhesion/aggregation; therefore, alterations in blood flow and platelet function due to a lack of NO may result in thrombosis [26]. One study of over 400 SAH patients concluded that NO may mediate the association between RBCT and angiographically confirmed vasospasm [27]. Therefore, RBCT employed to minimize DCI may unwittingly predispose to it.

Storage-related changes have also been implicated in the development of thrombosis after RBCT. Prolonged storage of RBCs was associated with an increased risk of DVT in a cohort of trauma patients [17]. Free iron, found in high concentrations in stored blood, has been associated with oxidative stress via formation of free radicals. This type of damage has been associated with cardiovascular disease. Free hemoglobin can also bind and inactivate nitric oxide (NO), which may lead to vasoconstriction [28]. Anucleoid membrane vesicles, or microparticles, increase in concentration with storage duration. Microparticles have been implicated in post-transfusion thrombosis via plasma-mediated thrombin generation [29]. However, despite these plausible mechanisms, age of blood was not identified as a risk factor for the development of TE in our study. The conflicting data may be due in part to the effect of leukoreduction, as white blood cells have been implicated as the primary cause of deleterious storage-related changes [30, 31].

At the time of this study, the institutional SAH protocol called for maintenance of hemoglobin concentration above 10 g/dL. Such a liberal threshold may not be warranted as it may promote thrombosis via augmented blood viscosity, amplified turbulent flow, and increased platelet interactions, as previously mentioned. However, the optimal transfusion threshold for patients with SAH remains unclear [32]. Therefore, we propose that clinical equipoise remains regarding transfusion thresholds for those patients at risk for cerebral ischemia; current recommendations advocate for maintaining hemoglobin levels between 8 and 10 g/dL [33].

This study's findings are both robust and noteworthy. The effect of transfusion on TE was found to be dose-dependent and it persisted in multivariable analysis after controlling for several potential confounders. Furthermore, the magnitude of the association is large. In subgroup analysis, the adjusted odds ratios of RBCT on VTE and cerebral infarction risk remained significant [2.4 [95 % CI (1.0, 5.4) $p = 0.04$] and OR 2.2 95 % CI (1.1–4.1); $p = 0.01$] despite fewer outcomes. The effect of RBCT was also independent of other blood product administration.

Our study has some significant limitations, chief among them are the definition and determination of TE. The definition of cerebral infarction after SAH as a thrombotic event implies a thromboembolic etiology, although it may result from arterial vasospasm. However, the mechanisms of DCI and the etiology of cerebral infarction after SAH remain unclear. Therefore, we believe that it was reasonable to consider cerebral infarction a TE given our working hypothesis and the aforementioned evidence that SAH is associated with a hypercoagulable state. Moreover, the association persisted in subgroup analysis of VTE, suggesting that the mechanism is plausible. Second, surveillance Doppler ultrasounds were performed twice weekly, a protocol designed to protect neurologically injured patients from the consequences of VTE. However, this protocol may have lead to an ascertainment bias. Moreover, the observed rate of DVT was almost double the previously published rates; however, this may reflect the local surveillance policy or the increased acuity of illness at our institution, a dedicated hospital for vascular neurosurgery [34]. Although this may limit the generalizability of the results, it does not mitigate the observed association between RBCT and thrombosis. Third, diagnostic testing for other TE was limited to that clinically indicated by the treating physician. Therefore, investigation of non-DVT TE was only undertaken when deemed clinically indicated and subclinical TE may have gone unrecognized.

Confounders may also limit generalizability of this study. Due to its retrospective design, the study may be confounded by unmeasured parameters and, therefore, cannot confirm causality. Anemia, a marker of disease severity, may confound by intention as anemic patients warrant transfusion. However, rates of premorbid anemia, defined by admission hemoglobin concentration, were not significantly different among those patients with and without TE. Similarly, although surgical intervention significantly affected likelihood of transfusion, in multivariable analysis, it had no effect on thrombosis risk. Injury severity as assessed in this study may not adequately account for the greater burden of comorbidities, systemic complications, or severe immobility, which may contribute to thrombosis risk in ICU patients. However, the effect of transfusion on TE persisted in multivariable analysis when accounting for both Hunt and Hess grade and length of stay, established surrogates for severity of illness.

Conclusions

Our data suggest that RBCT is associated with increased risk of TE in patients with SAH. This adds to the growing body of literature suggesting that RBCT in critically ill patients is not a benign intervention and must be administered with caution. It appears that age of blood is not a significant factor in thrombotic risk, possibly due to routine leukoreduction in our cohort. These data may support the existence of a transient hypercoagulable state after SAH. Larger prospective studies are required to further investigate this association.

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