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The Deleterious Effect of Red Blood Cell Storage on Microvascular Response to Transfusion

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Abstract

Background—The transfusion of relatively older red blood cells (RBCs) has been associated with both morbidity and mortality in trauma patients in observational studies. Although the mechanisms responsible for this phenomenon remain unclear, alterations in the microcirculation as a result of the transfusion of relatively older blood may be a causative factor. To assess this hypothesis, we evaluated microvascular perfusion in trauma patients during RBC transfusion.

Methods—Anemic but otherwise stable trauma ICU patients with orders for transfusion were identified. Thenar muscle tissue oxygen saturation (StO₂) was measured continuously by near infrared spectroscopy during the course of transfusion of one RBC unit. Sublingual microcirculation was observed by sidestream dark field illumination microscopy before and after transfusion of one RBC unit. Thenar muscle StO₂ was recorded over the course of transfusion. Pre- and post-transfusion perfused capillary vascular density (PCD) was determined by semi-quantitative image analysis. Changes in StO₂ and PCD relative to age of RBC unit were evaluated using mixed models that adjusted for baseline StO₂ and Spearman's correlation, respectively.

Results—Overall, 93 patients were recruited for study participation, 69% were male and average Injury Severity Score was 26.4. Average pre-transfusion hemoglobin was 7.5 mg/dL and the average age of RBC unit transfused was 29.4 days. Average peri-transfusion StO₂ was negatively associated with increasing RBC age (slope -0.11, $p = 0.0014$). Change in PCD from pre- to post-transfusion was found to correlate negatively with RBC storage age (Spearman correlation = -0.27, $p = 0.037$).

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Conclusions—The transfusion of relatively older RBC units was associated with a decline in both StO₂ and PCD. Collectively, these observations demonstrate that transfusions of older RBC units are associated with the inhibition of regional microvascular perfusion. In patients requiring multiple units of RBCs, alteration of the microcirculation by relatively older units could potentially contribute to adverse outcomes.

Level of Evidence: II, prognostic study

Introduction

Over the past century, advances in blood storage have culminated in the capacity to store red blood cells (RBCs) for up to six weeks prior to transfusion. Nevertheless, it is well known that changes occur during RBC storage, resulting in structural and functional defects collectively referred to as the red cell storage lesion.¹ The 42-day expiration date for RBC units is based on regulations that specify only two requirements: (1) 75% of the RBCs remain in the circulation at 24 hours after transfusion and (2) hemolysis in the storage bag does not exceed 1%. Although 42 day-old RBCs meet this standard, a significant number of laboratory and clinical studies have raised concerns that relatively older, but not expired RBCs may not be as safe for transfusion as RBCs stored for a shorter duration.²⁻⁹

Although some clinical studies suggest that there is no harm associated with the transfusion of relatively older RBC units¹⁰⁻¹², an expanding body of clinical research suggests otherwise, demonstrating associations between the transfusion of older RBC units and both morbidity and mortality.^{5,13} Among trauma patients, death, pneumonia, renal failure, and extended length of stay have been demonstrated to be associated with the transfusion of older RBCs.¹⁴

The corresponding pathophysiologic mechanisms to explain the deleterious effect of older RBC transfusions have yet to be clearly defined. We theorize that the transfusion of relatively older RBCs may be injurious to patients as a result of a negative effect on microvascular perfusion. Observation of the sublingual microcirculation during transfusion may be performed at the bedside with sidestream dark field (SDF) microscopy.^{15,16} Tissue oxygen saturation (StO₂), as measured by near-infrared spectroscopy, is also measurable at the bedside, and has been demonstrated in a multi-center study to identify poor perfusion and predict multi-organ dysfunction and death in trauma patients.¹⁷ Using these technologies, we evaluated the microcirculation in trauma patients to determine if, in fact, transfusion of relatively older RBCs was associated with a decrease in perfusion.

Methods

A prospective cohort study was carried out between September 2009 and July 2012 at two level I academic trauma centers. Study approval was obtained from the Institutional Review Boards of the University of Alabama at Birmingham (UAB) and the University of Tennessee Health Science Center (UT).

Study population

Over the period of study, patients in the trauma intensive care unit with orders to receive RBC transfusion were screened for participation. Study inclusion criteria included admission to the trauma intensive care unit from the emergency department (directly or by way of the operating room or angiography suite) following blunt or penetrating injury. Patients who were receiving transfusion in the context of volume resuscitation were excluded from participation. Patients who were receiving vasopressors or were otherwise hemodynamically unstable were also excluded from participation. Additional exclusion criteria included pregnancy, age less than 19 years, and burn injuries. Patients were enrolled in the study following obtainment of informed consent from the patient or patient's legally authorized representative.

The decision to transfuse was made by the attending physician prior to and independently of the patient's participation in the study. There was no protocol in place related to the indication for transfusion that was specific to the study. During the study period, all RBC units transfused had undergone pre-storage leukoreduction within 24 hours of collection by high-efficiency filters. The storage duration (days) for each unit transfused was recorded.

Variables of interest

Enrolled patients underwent evaluation of the microcirculation by way of sublingual video microscopy and near infrared spectroscopy of the thenar muscle bed. Sublingual microscopy was performed with a handheld video microscope (MicroScan BV, Amsterdam, The Netherlands). This device captures video images of the sublingual microcirculation with SDF illumination technology. The details regarding this technique have been reported elsewhere.¹⁸ The device was applied to the sublingual capillary bed, and three to five separate images of approximately 20 seconds duration each were recorded at three time points: immediately prior to transfusion of a single red blood cell unit, immediately following transfusion of the RBC unit, and one hour following completion of the transfusion.

Video images were later evaluated by an observer blinded to both study patient and image sequence (i.e. pre- vs. post-transfusion). Perfused capillary density (PCD) as described by De Backer et al was determined.¹⁹ In brief, a grid consisting of three equidistant horizontal and vertical lines was placed over the video image. Capillary vascular density was discerned by counting the number of small vessels (< 20 micrometers) that cross the lines divided by the total length of the lines. PCD was calculated by determining the fraction of the number of small vessels with visualized flow that cross the lines.

A near infrared tissue spectrometer was used to record StO₂ values (Hutchinson Technology, Hutchinson, MN). The spectrometer was placed on either the left or right thenar eminence (if a radial arterial line was present, the opposite hand was used for StO₂ monitoring). StO₂ monitoring was initiated approximately 10 minutes prior to starting RBC transfusion, and was discontinued one hour following the completion of the transfusion. StO₂ measurements were recorded at two-second intervals and were averaged for every two-

minutes of observation from the beginning of transfusion until 1-hour post-transfusion, approximately 2 hours of observation.

Other variables included demographic (age, gender), injury (blunt versus penetrating mechanism, and injury severity score (ISS)), and hospitalization (hospital days, ICU Days, ventilator support days, and in-hospital mortality) characteristics. In addition, pre-transfusion clinical data (hemoglobin, serum lactate, base excess, and mean arterial pressure) measured on the day of study participation was recorded.

Statistical analysis

Differences in PCD between transfusion time points were evaluated with nonparametric measures of comparison. Specifically, correlations between RBC storage age and changes in PCD were assessed by Spearman – rho, a correlation comparison based on ranks. The repeated measures analysis of StO₂ utilized mixed models and evaluated the association between RBC storage age and StO₂ over the duration of the transfusion period. The mixed models included subjects' baseline StO₂ values, adjusting for pre-transfusion StO₂. Resulting beta parameters represent the effect of the predictor variables, i.e., baseline StO₂ and blood age, on StO₂. Finally, the association between StO₂ and a number of potential confounders, including time of StO₂ measurement, institution (UAB versus UT), sex, age, injury mechanism, (blunt versus penetrating), ISS, and pre-transfusion mean arterial pressure and hemoglobin, were evaluated similarly with mixed models that adjusted for patients' baseline StO₂. SAS version 9.2 (Cary, NC) was used for the statistical analysis.

Results

Overall, 93 patients were enrolled in the study. The characteristics of the study group are demonstrated in Table 1. All patients were in an intensive care unit at the time of study enrollment and all had severe injuries (mean Injury Severity Score of 26.4). In-hospital mortality for the cohort was 5.4%.

Table 2 demonstrates clinical data pertaining to the day of study participation. All patients were hemodynamically stable without the support of any vasopressors, and all were anemic (average hemoglobin, 7.5 g/dL). The average base excess was 3.2 mmol/L. No patient had received any transfusions on the day of study before study enrollment. The age of RBC unit transfused ranged from 7 to 42 days, with an average age of 29.

Sublingual microcirculation was observed in 62 patients. Adequate video microscopy images were either not obtainable or of sufficient quality secondary to patient cooperation in the remaining patients. Pre-transfusion PCD ranged from 1.8 to 18.4 n/mm, with a median of 9.2 n/mm. Immediately post-transfusion, the median PCD was 8.3 n/mm (range 3.9 to 18.7 n/mm), and 1-hour post-transfusion, the median PCD was 12.9 n/mm (range 5.8 to 22.2 n/mm). The change in PCD from pre-transfusion to immediately post-transfusion ranged from -6.2 to 4.5 n/mm and was found to correlate negatively (Spearman correlation = -0.266, $p = 0.564$), with RBC storage age (Figure 1). The change in PCD from pre-transfusion to 1-hour post-transfusion ranged from -6.3 to 7.6 n/mm and was not significantly correlated with RBC storage age (Spearman correlation = -0.076, $p = 0.564$).

Continuous StO₂ measurements were recorded for 81 patients over the peri-transfusion period. In the remaining patients, monitoring was hindered by inadequate sensor adherence to the patient's hand during the entire observation period or similar technical problems. Results of the mixed model used to examine the association between StO₂ and RBC age over the transfusion period, i.e., from the beginning of transfusion to one-hour post-transfusion (Table 3) demonstrates that with each increase in day of blood storage age, the StO₂ decreased by 0.1064 ($p=0.0012$). The model predicts a progressive decline in overall StO₂ of approximately 0.11% for each day of blood age (Figure 2). Table 3 also presents results for potential confounders that were evaluated similarly; no significant association was found for any of the variables examined.

Discussion

In clinical practice, the underlying goal of RBC transfusion is the maintenance of tissue oxygen delivery. Nonetheless, there is a notable lack of evidence for this desired effect, and, in fact, a growing body of work suggests that stored RBCs may have adverse effects on microcirculatory flow and oxygen utilization. Raat et al. demonstrated that RBCs stored for longer periods of time (5 weeks) resulted in diminished oxygen delivery to the gut microcirculation of anemic oxygen-supply dependent rats. In contrast, relatively fresh RBCs, stored only several days, and intermediate-aged RBCs, stored several weeks, both improved oxygen delivery.²⁰ Similarly, Fitzgerald et al. demonstrated that RBCs stored for 28 days did not improve oxygen delivery and consumption when transfused to rats while transfusion of blood stored only 3 days did, in fact, improve oxygen delivery.²¹

In human studies, observations have been less conclusive. Marik et al. observed a decreased gastric pH, a surrogate measure of gastric mucosal oxygenation status, in patients receiving blood that had been stored beyond 15 days.²² Walsh et al., however, were unable to replicate the results of Marik et al, which were identified in the course of *post hoc* analysis. In a prospective, double-blind trial of critically ill intensive care unit patients randomized to receive leukodepleted red cells stored either 5 days or 20 days, Walsh et al. observed no significant differences in gastric pH measurements or other indices of global tissue oxygenation.²³ More recently, Kiraly et al. evaluated peripheral tissue oxygenation as measured by near infrared spectroscopy during the course of red cell transfusion.²⁴ The authors observed that patients transfused with blood stored 21 days or longer had a statistically significant decline in tissue oxygen saturation compared with those transfused with blood less than 21 days old.

Similar to the findings of Kiraly et al.²⁴, the results of the present study demonstrate that transfusion of older RBC units was associated with inhibition of microvascular perfusion and/or oxygen delivery as evidenced by degradation in both functional capillary density and tissue oxygen saturation. The clinical relevance of these collective observations is unclear, as the magnitude of the changes observed in PCD in the present study and StO₂ in both this study and the work of Kiraly et al., while statistically significant, are relatively small. Nonetheless, these observations do provide some basis for causation with respect to the growing body of observational studies that demonstrate an association between the transfusion of older blood and mortality. Wang et al. recently performed a meta-analysis of

21 studies (409,966 patients) concerning the transfusion of older blood and the risk of death, and found that older blood was associated with a significantly increased risk of death (odds ratio 1.16; 95% confidence interval 1.07 - 1.24).⁵ In our own observational trauma patient studies, we identified that both storage age and number of units transfused to acutely injured patients were independently associated with mortality.^{3,4} We speculate that in relatively unstable patients requiring multiple units of blood, the vasoconstrictive effect at the level of the microcirculation potentiated by older stored RBCs is a primary factor related to adverse outcome.

The mechanisms pertaining to storage lesion toxicity continue to be explored by our group and others. It is now appreciated that in addition to transporting oxygen to tissues, the red cell also functions as an oxygen sensor and transducer of vascular tone, mediated by interactions with nitric oxide (NO).²⁵ Aged stored RBCs are thought to interfere with nitric oxide homeostasis.²⁶⁻²⁸ We have recently demonstrated in competition kinetic analyses that consumption rates of NO increased $\square$ 40-fold and NO-dependent vasodilation was inhibited 2–4-fold comparing 42-day-old with 0-day-old RBCs.⁶ These results are probably due to the formation of smaller RBCs with increased surface area:volume as a consequence of membrane loss during storage. Associated with this was a significant loss of whole-blood nitrite that was observed in trauma patients after transfusion of 1 RBC unit, with the decrease in nitrite occurring after transfusion with RBCs stored for >25 days, but not with younger RBCs. Other groups have proposed that NO is scavenged by microparticles and free hemoglobin that accumulate during storage. Recently, Solomon et al., utilizing a canine pneumonia experimental model, observed that mortality was significantly higher among the dogs transfused 42 day-old stored RBCs compared with those who received 7 day-old RBCs.² Other differences between the two groups included higher plasma cell-free hemoglobin and nitric oxide (NO) consumption capability, and lower haptoglobin levels in the older RBC group, suggesting that older RBCs have a propensity to hemolyze in vivo following transfusion, releasing vasoconstrictive cell-free hemoglobin. In our complement studies, we have observed that C5b-9 levels in stored RBC units significantly increased as a function of storage time and were associated with increases in free hemoglobin levels, suggesting the possibility of a complement-mediated storage toxicity.

There are several limitations worth noting concerning the present study. The study cohort comprises relatively few patients that received “younger” blood (only two patients received RBC units less than two weeks old). As previous clinical outcome studies have defined old versus young RBC units with a 14-day cutpoint,³⁻⁵ it would have been informative to have younger RBCs better represented in the current study. Nonetheless, our study was strengthened by a repeated measures approach that dramatically increased the number of observations available for estimating a relatively small linear effect of decreasing StO₂ with increasing blood age; the potential cumulative effect, however, approaches a 4.5% decrease in oxygen saturation (i.e., -0.1064×42 days). Analysis of the sublingual microcirculation by microscopy is semiquantitative by nature. Although both intra- and interobserver variability has been reported to be relatively low in validation studies (around 5-10%)²⁹, it is possible that such variability limits the reliability of the data analysis. Although we evaluated two separate tissue beds, the lack of sufficient paired data as a result of not all patients having

data from both StO₂ monitoring and sublingual microscopy precluded a sufficient paired-data analysis. In roughly one-third of the study patients, adequate video microscopy images were either not obtainable or of sufficient quality secondary to patient cooperation, and occasionally StO₂ monitoring was hindered by inadequate sensor adherence to the patient's hand during the entire observation period or similar technical problems. An additional limitation of the present study pertains to baseline variability in the microcirculation from patient to patient, prior to transfusion. In previous work, we identified the fact that among a cohort of seemingly resuscitated, hemodynamically stable trauma patients, pre-transfusion sublingual perfusion was quite variable, and those patients with relatively poor sublingual perfusion were more likely to respond favorably to transfusion (i.e. a post-transfusion improvement in perfusion), whereby those patients with relatively normal pre-transfusion perfusion tended to demonstrate either no change or, in fact, a deterioration of sublingual perfusion following RBC transfusion.¹⁶ To address this concern, a Spearman partial correlation, adjusting for pre-transfusion PCD, was carried out; the resulting correlation between blood age and change in PCD had a magnitude and direction ($\rho=-0.22316$) consistent with the unadjusted result; however, the correlation was no longer statistically significant ($p=0.0839$), suggesting that a small sample size influenced significance. It is also notable that the change in PCD related to RBC storage age was found to be both of relatively small magnitude and not sustained at one-hour post transfusion. Underlying differences between study patients, including interval from initial injury, presence or absence of infection, and variation in administration of intravenous fluids and medications may contribute to the variability observed in PCD measurements, as routine clinical care was not altered during the observed transfusion. Lastly, it is known that the Inspectra StO₂ monitoring device cannot distinguish between hemoglobin and myoglobin.³⁰ A relative muscle perfusion deficit may result in interference with accurate measurement of StO₂. This would not be expected to be a significant problem in this relatively stable study cohort, but could potentially be an underlying issue with respect to accuracy of StO₂ measurement.

In summary, we have observed changes in the sublingual microcirculation and in the muscle tissue oxygen saturation related to the transfusion of relatively older blood in a hemodynamically stable, but anemic trauma patient cohort. These observations lend pathophysiologic support to clinical studies that demonstrate adverse consequences of RBC transfusion related to storage age. RBC transfusion is often performed in an effort to augment tissue oxygen delivery, but this therapy may in fact be inhibitory to tissue perfusion. Although the transfusion of a single RBC unit of relatively advanced storage age is unlikely to have any negative clinical effect, we speculate that for patients requiring multiple units of RBCs, the compounding impact of older RBCs on microcirculatory dysfunction could contribute to adverse post-injury outcomes.

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Figure 1.

Scatter plot representing RBC storage age (days, x-axis) and the change in PCD (n/mm, y-axis) immediately post-transfusion. Spearman correlation = -0.266, $p = 0.037$.

Figure 2.
Predicted average StO₂ over the duration of transfusion as related to RBC age (based on pre-transfusion StO₂ of 74%).

Table 1

Demographic, injury, and hospitalization characteristics of study subjects (n=93), as well as single unit RBC age. Values reported as mean (SD) unless otherwise stated.

Demographic	
Age, years	46.5 (20.07)
Male (%)	64 (68.8)
Institution	
UAB	36 (38.7)
UT	57 (61.3)
Injury	
Mechanism (%)	
Blunt	71 (76.3)
Penetrating	22 (23.7)
Injury Severity Score	26.4 (14.23)
Hospitalization	
Hospital Days	37.3 (30.79)
ICU Days	26.3 (28.24)
Ventilator support Days	21.9 (28.68)
In-hospital Mortality (%)	5 (5.4)

Table 2

Clinical characteristics of study cohort at time of study participation (n=97). Values reported as mean (SD).

Pre-transfusion Hemoglobin (g/dL)	7.5 (0.86)
Serum Lactate (mmol/L)	1.1 (0.60)
Base Excess (mmol/L)	3.2 (4.54)
Mean Arterial Pressure (mm Hg)	85.6 (12.28)

Table 3

Associations between peri-transfusion StO₂ and predictor variables; adjusting for patient baseline StO₂.¹

Adjusted for baseline StO ₂		
Predictors	Beta	p-value
Time	0.0254	0.9229
Center (UAB versus UT)	0.6551	0.2526
Blood age (days)	-0.1064	0.0012
Female versus male	0.6306	0.2974
Age (years)	-0.0049	0.7353
Blunt versus penetrating mechanism	0.8344	0.2089
Injury severity score	0.0333	0.0929
MAP	-0.0089	0.3239
Pre Hemoglobin	0.0449	0.7657
Base deficit	-0.1329	0.2345

¹ Model: Average %O₂ = Baseline O₂ + predictor