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Older red cell units are associated with an increased incidence of infection in chronically transfused adults with sickle cell disease

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ABSTRACT

Background: In adults with sickle cell disease (SCD), the effects of the red cell storage lesion are not well defined. The objectives of this study were to: (1) describe the distribution of storage ages provided to adults with SCD, and (2) evaluate clinical outcomes associated with storage age.
Patients and methods: We performed a retrospective cohort study of adults with SCD managed with prophylactic simple transfusion regimens. Units were universally pre-storage leukocyte reduced and CEK-matched. Age of the unit was 42 days minus the difference between the expiration and transfusion dates. A mixed effects model, which accounts for a subject's contribution to repeated transfusion encounters, was used to investigate the association between storage age and the incidence of hospital encounters for infection and pain crises prior to the next red cell transfusion.
Results: Over the study interval, twenty-eight steady-state adults with SCD received 627 units via simple transfusion over 281 outpatient encounters. Overall median unit storage age was 22 days (range: 2–42 days). Receipt of older units was associated with an increased incidence of emergency department or hospital admission for infection prior to the next transfusion ($p = 0.04$). There was no association between unit storage age and admission for pain ($p = 0.4$).
Discussion: In a cohort of chronically transfused adults with SCD, we provide evidence that receipt of older units is associated with a higher rate of admission for infection. Prospective studies will need to validate these data and explore potential mechanisms by which these older units promote infection.

1. Introduction

Red cell transfusions are the most critical therapy to reduce morbidity and mortality in patients with sickle cell disease (SCD) [1]. For decades, transfusions have been used to reduce hemoglobin S percentage in order to treat acute complications, such as severe anemia, stroke, acute chest syndrome (ACS) and multi-organ failure [1–3]. More recently, however, there has been a greater dependence on scheduled transfusions, administered usually on a monthly basis, in order to lessen and hopefully prevent the complications of SCD [4]. Well-established is the use of chronic transfusions for the indication of secondary stroke prevention [5], but chronic transfusions are now also used for primary stroke prevention in children with elevated transcranial doppler velocities [6], for silent cerebral infarcts to prevent additional strokes [7], as well as for the prevention of frequent or severe vaso-occlusive episodes [7–10]. Although transfusions are a cornerstone of therapy, few guidelines exist as to what constitutes the optimal red cell unit for a patient with SCD. Recent NIH guidelines recommend phenotype-matched units for C, E, and Kell, but do not address age of blood, even though some blood bank directors consider storage age to be an important factor [1,11].

The refrigerated storage of red cell units result in a well-established array of biochemical changes referred to as the "storage lesion" [12,13]. In addition to the release of potentially harmful by-products of lysed red cells (potassium, cell-free hemoglobin, reactive oxygen species) into the plasma of older units, important changes also occur in intact red cells [12,13]. Key mediators of red cell function, such as adenosine triphosphate and 2,3 diphosphoglycerate (2,3-DPG), significantly decrease with increased storage time, which may affect blood flow and oxygen delivery of older units [12,13]. There are also changes to red cell membranes, with subsequent decreases in red cell deformability and often aberrant surface exposure of phosphotidylserine (PS), a

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phospholipid normally sequestered in the inner red cell membrane [14,15]. PS is known to promote phagocytosis of older red cells, which may be particularly detrimental when a bolus of older red cells is transfused in one or several units [16–18]. The excess of red cells may overwhelm the metabolic capacity of phagocytes and promote the release of toxic heme and non-transferrin bound iron (NTBI) into circulation [19,20]. In pre-clinical models, excess NTBI has been associated with the fatal proliferation of ferrophilic bacteria [21–24].

Because the physiology promoted by the red cell storage lesion shares features with SCD (increased cell-free hemoglobin, reactive oxygen species (ROS) and NTBI), older units may exacerbate an already-present pathobiology [25–30]. Reduced nitric oxide (NO), secondary to cell-free hemoglobin, and increased ROS may promote vaso-occlusion with higher rates of pain and ACS [27,25,26]. Incidence of infection, already high due to functional asplenia, could also be increased further due to free heme and NTBI [31–33]. Despite the storage lesion's potential for harm in SCD, only three observational studies and one prospective trial have been conducted. In the observational studies, receipt of older units were associated with alloimmunization and vaso-occlusion [28–30]. The only prospective trial, conducted in severely anemic African children with malaria ($N = 251$) and SCD ($N = 39$), found no difference in the ability of older versus younger units to correct lactate levels [34]. However, since the study was comprised mostly of children with malaria and the focus was oxygen delivery in an emergency setting, the study may not be relevant to the most common indication for transfusion in SCD: to lower S percentage as part of a chronic transfusion program.

To determine whether storage age is associated with adverse outcomes in chronically transfused, steady-state adults with SCD, we performed a retrospective cohort study. The objectives were to: (1) define the distribution of storage ages provided to this population at our institution, and (2) determine the clinical outcomes associated with the transfusion of older stored units.

2. Methods

This study was approved by the institutional review board at Froedtert Hospital and Medical College of Wisconsin (FH/MCW). We performed a retrospective study of adults with SCD who received simple transfusions as part of a chronic transfusion protocol for severe chronic pain or previous stroke.

2.1. Data collection

Inclusion criteria: (1) a diagnosis of SCD, (2) ≥18 years of age, (3) treatment with a chronic red cell transfusion protocol during January 1, 2012–December 31, 2014, and (4) outpatient transfusions. Exclusion criteria: (1) receipt of washed or irradiated units, and (2) automated exchanges. The demographics, red cell transfusion history and emergency department/hospital admissions of adults who met criteria were identified by a systematic search of the electronic medical record and recorded on case report forms. The age of the RBC unit was calculated by taking 42 days minus the difference between the expiration and transfusion dates. Hemoglobin (g/dl) and hemoglobin S% was recorded pre- and post-red cell transfusion when available in the electronic medical record. Change in hemoglobin and hemoglobin S% per day was the difference between the post- and pre-transfusion values, divided by the number of days between lab measurements. Patient ferritin was defined as the first outpatient ferritin measured during the study period that was at least 4 weeks from a recent hospital or ED admission.

2.2. Red cell unit characteristics

Units at our institution are pre-storage leukocyte reduced, and preserved predominantly in AS-1, AS-3, or AS-5 storage solution (CPDA-1 represented <3% of the total transfused inventory, and for this study were treated as AS units), and all red cell units are prophylactically-matched for ABO/Rh (D,C,c,E,e), and K antigens. Additional antigen matching occurred in cases when other clinically significant alloantibodies are identified (i.e. anti-Jk, -Fy, or -S). Units are universally tested as sickle negative in the blood bank prior to the release of the unit to the patient. Per transfusion service protocol, simple transfusions can be of any storage age so long as they meet the previously noted antigen-matching and sickle negative requirements. In contrast, our institution limits blood storage age to less than 15 days in those with automated exchanges, which is why they were not included in this study.

2.3. Key definitions

1) *Vaso-occlusive pain crisis:* an episode of acute pain with no cause other than a vaso-occlusive event lasting at least 24 h that requires the administration of oral or parenteral opioids in a medical facility [35].
2) *Acute chest syndrome:* an acute illness requiring medical facility attention characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray [36].
3) *Acute infection:* any acute illness requiring medical facility evaluation and intervention and characterized by infectious symptoms defined by the Common Terminology Criteria for Adverse Events (CTCAE) as used by the recently published RECESS trial [37,38]. When infection and pain occurred concurrently, the admissions were counted as infection.
4) *Chronic transfusion*: receiving red cell units on a 4–8 week schedule as part of routine, non-acute care.

2.4. Data analysis

Demographic variables were presented as percentages for categorical variables and medians with interquartile ranges (IQR) for continuous variables. A Chi-square or Fisher's exact test was used to examine the associations between patients' infection status (patients who developed infection during the study period vs. patients who did not) and categorical variables. Differences between groups were analyzed with a Mann–Whitney–Wilcoxon test, whereas Pearson correlation coefficients were calculated for the correlation between patients' age and average age of blood units per patient. We limited our evaluation to only outpatient transfusion encounters, since, if patients were transfused in hospital, hospital-related illnesses could have confounded our ability to detect subsequent admissions related to age of blood [39]. Only emergency department (ED) or hospital admissions that occurred after an outpatient transfusion encounter and prior to the next documented red cell transfusion for an individual patient were included in the analyses. A mixed effects model, accounting for an individual subject's contribution to repeated transfusion encounters, was then used to investigate the association between storage age and the incidence of hospital encounters for infection and vaso-occlusive pain. Average unit age of the red blood cell or categorized unit age of the red blood cell (All> = 25 days, At least one >25 days, and All <25 days), days between transfusions, average unit age by days between transfusion interactions, and ferritin were included in the model. The intercept was modeled as random. A random coefficient model with unstructured covariance structure was used to examine the association between average unit age of the red blood cell and the interval decrease in hgb/day or the interval increase