Transfusion and Apheresis Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

# Mathematical calculation of lifespan of transfused RBCs in sickle cell disease patients

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ARTICLE INFO

*Article history:*
Received 24 August 2017
Accepted 19 November 2017
Available online xxx

*Keywords:*
Sickle cell disease
Transfusion
Erythrocyte survival
Mathematical model

ABSTRACT

*Background:* Transfusion of donor red blood cells (RBCs) remains an important part of management of sickle cell disease (SCD). However, the survival characteristics of transfused donor RBCs in SCD patients have not been well studied. We sought to calculate survival kinetics of transfused RBCs in SCD patients since it is unclear whether transfused RBCs get destroyed at faster rate as innocent bystander or persist longer due to decreased destruction capacity such as functional splenectomy.
*Study design:* and methods Forty-one SCD patients who had undergone at least 3 RBC exchange procedures were inlcuded. Interval between the procedures, both pre-procedure and post procedure hematocrits, HbA% and HbS% were collected. We developed a mathematical model to calculate RBC lifespan for donor RBCs.
*Results:* Donor RBCs exhibited average lifespan of about 120 days (121.1 ± 13.9 days), which was similar to reported survival of RBCs in normal recipients. However, significant variation between patients were observed with lifespan ranging from 75.6-148.5 days. Intrapersonal variations were small in most cases.
*Conclusion:* The calculated survival of donor RBCs in SCD recipient, based on certain laboratory values, appears to be similar to that of normal recipient. However, inter-personal variations were large, suggesting different RBC kinetics in a subset of patients, which calls for further research to better understand underlying pathophysiology. This knowledge of RBC survival would be very helpful in individualized management of patients on chronic RBCx.



## 1. Introduction

Transfusion of donor red blood cells (HbA RBCs) is an important part of the management plan for sickle cell disease (SCD) patients. In patients with stroke or other recurrent sickle cell crises, chronic RBC exchange (RBCx) remains a standard of care therapy to avoid iron overload and reduce frequency of hospital visits. However, despite widespread use of transfusion in the management of SCD, survival kinetics of transfused HbA RBCs in SCD patients remain unclear. The lifespan of RBCs in SCD patients (HbS RBCs) [1], RBCs in healthy volunteers [2] or that of transfused RBCs in normal recipients [3,4] have been studied earlier. However, several factors such as difference between HbS and HbA RBCs physiology, vasculopathy, high level of hemolysis of HbS RBCs and change of splenic function in SCD patient preclude extrapolation from currently available RBC survival data to transfused HbA RBCs in SCD patients. While metabolic and labeling studies have been useful in the study of RBC survival, these methods have limitations such as requirement of additional intervention, the use of specialized equipment and collection of additional samples.

We have over 40 patients in our chronic RBCx program. Some of these patients maintain interprocedure intervals of 8–9 weeks whereas other maintain only 4–5 weeks to achieve our target HbS values and Hct. Since this observed variations could be due to difference in RBC survival kinetics, we sought to develop a simple mathematical model to estimate HbA RBC survival in SCD patients undergoing chronic RBCx, using routinely available laboratory data such as hematocrit, HbA percentage and HbS percentage. We selected well established patients undergoing chronic RBCx and calculated HbA RBC lifespan to study intrapersonal differences in RBC lifespan in addition to interpersonal comparison.

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https://doi.org/10.1016/j.transci.2017.11.029
1473-0502/

**A**

RBCx 0, -1 and -2 = Sequence of RBCx (RBCx 0 being most recent and RBCx -2 being earliest procedure)

$T_1$ = Interval between RBCx 0 and RBCx -1

$T_0$ = Interval between RBCx -1 and RBCx -2

$\Delta$ = Decrease in HbA RBC mass between RBCx -1 and RBCx 0

= Post-RBCx -1 (Total blood volume(or TBV) · Hct · HbA %) – Pre-RBCx 0 (TBV · Hct · HbA %)

$A_{New}$ = HbA RBC mass transfused during RBCx -1

= Post-RBCx -1 HbA RBC mass · (1 – Fraction of cells remaining(FcR))

$$= \text{Post-RBCx -1 (TBV} \cdot \text{Hct} \cdot \text{HbA \%)} \cdot \left(1 - \frac{\text{Post–RBCx –1 HbS mass}}{\text{Pre–RBCx –1 HbS mass}}\right)$$

$$= \text{Post-RBCx -1 (TBV} \cdot \text{Hct} \cdot \text{HbA \%)} \cdot \left(1 - \frac{\text{Post–RBCx –1 (TBV} \cdot \text{Hct} \cdot \text{HbS \%)}}{\text{Pre–RBCx –1 (TBV} \cdot \text{Hct} \cdot \text{HbS \%)}}\right)$$

$A_{old}$ = HbA RBC mass transfused from RBCx -2 remaining after RBCx -1

= Post-RBCx -1 HbA RBC mass · FcR

$$= \text{Post-RBCx -1 (TBV} \cdot \text{Hct} \cdot \text{HbA \%)} \cdot \frac{\text{Post–RBCx –1 (TBV} \cdot \text{Hct} \cdot \text{HbS \%)}}{\text{Pre–RBCx –1 (TBV} \cdot \text{Hct} \cdot \text{HbS \%)}}$$

**B**

$\Delta = k \cdot T_1$ ; Change in HbA mass = Rate of HbA destruction multiplied by time (RBCx interval)

$$\Delta = \left(\frac{A_{New}}{L} + \frac{A_{old}}{L - T_0}\right) \cdot T_1 \quad ; \text{Rate of HbA destruction} = \frac{\text{New HbA mass}}{\text{RBC lifespan}} + \frac{\text{Old HbA mass}}{\text{Remainig RBC lifespan}}$$

$$\Delta \cdot L \cdot (L - T_0) = A_{New} \cdot (L - T_0) \cdot T_1 + A_{old} \cdot L \cdot T_1 \quad ; \text{Multiplied both sides with } L \cdot (L - T_0)$$

$$\Delta \cdot L^2 - \Delta \cdot L \cdot T_0 = (A_{New} + A_{old}) \cdot L \cdot T_1 - A_{New} \cdot T_0 \cdot T_1$$

$$\Delta \cdot L^2 - (\Delta \cdot T_0 + A_{New} \cdot T_1 + A_{old} \cdot T_1) \cdot L + A_{New} \cdot T_0 \cdot T_1 = 0$$

By applying solution of quadratic equation $\left[x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}\right]$ for $(ax^2 + bx + c = 0)$,

$$L = \frac{(\Delta \cdot T_0 + A_{New} \cdot T_1 + A_{old} \cdot T_1) \pm \sqrt{(\Delta \cdot T_0 + A_{New} \cdot T_1 + A_{old} \cdot T_1)^2 - 4 \cdot \Delta \cdot A_{New} \cdot T_0 \cdot T_1}}{2 \cdot \Delta}$$

**Fig. 1.** A) Definition of variables and abbreviations. B) Derivation process of RBC lifespan. Briefly, the change in HbA RBC mass from Post-RBCx −1 to Pre-RBCx 0 is proportional to rate of HbA RBC destruction and the interval between RBCx −1 and RBCx 0 (line 1). HbA mass after completion of RBCx −1 was divided into two population namely $A_{New}$ and $A_{Old}$ (line 2). $A_{New}$ corresponds to HbA transfused during RBCx −1 while $A_{Old}$ corresponds to HbA transfused during RBCx −2. The amounts of RBCs reaching the end of lifespan will be inversely proportional to lifespan in $A_{New}$ while that of $A_{Old}$ will be inversely proportional to lifespan subtracted by interval between RBCx −2 and RBCx −1 ($T_0$) since RBCs in $A_{Old}$ will be at least $T_0$ days old (line 2). Equation has been modified to quadratic equation form in line 5 and solution is in line 7.

## 2. Materials and Methods

### 2.1. Population and data collection

Retrospective chart review was performed on fourty-seven patients who received RBCx (either standard RBCx or isovolemic hemodilution RBCx) during December 2014 and January 2017 after approval from University of Texas Southwestern Medical Center institutional review board. The study involved two sites (Parkland Memorial Hospital and Zale-Lipshy University Hospital, both affiliated with University of Texas Southwestern Medical Center, Dallas, TX). Procedures with missing data points or simple RBC transfusion between RBCx were excluded from the analysis. We included 41 patients who had at least 3 calculated RBC lifespans in the final analysis.

### 2.2. Mathematical analysis

Mathematical analyses were performed using specimen collection date, hematocrit, HbA percentage, HbS percentage from pre-RBCx and post-RBCx lab tests as raw data. List of variables calculated from raw data and used for analysis is summarized in Fig. 1A. Mathematical derivation of HbA RBC lifespan has been described in Fig. 1B. Briefly, change in HbA RBC mass was expressed as rate of RBC destruction multiplied by time between last RBCx (RBCx −1) and current RBCx (RBC 0). RBC destruction rate has been calculated by dividing RBC mass into those from previous procedure (RBCx −1) that has lifespan of HbA RBC remaining and RBC mass from earliest procedure (RBCx −2) with RBC lifespan shorter by the interval between RBCx −2 and RBCx −1 to reflect advanced RBC age. Equation has been transformed into quadratic equation form and then the solution for quadratic equation has been applied to calculate HbA RBC lifespan. While solution for quadratic equation yields two values, one value ranged from 20–50 days and the other value ranged from 70–150 days. The 20–50 day range is not consistent with clinical observation, as many of these patients present with HbS less than 50% after interval of 30-50 days. Therefore, the other value has been selected for further analysis. Supplementary data 1 contains a spreadsheet for calculation of RBC lifespan.

Please cite this article in press as: Kim J, et al. Mathematical calculation of lifespan of transfused RBCs in sickle cell disease patients. Transfus Apheresis Sci (2017), https://doi.org/10.1016/j.transci.2017.11.029