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Effect of stored blood in the critically ill

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Disclosure

- **Principal Investigator of ARIPI Trial assessing age of blood in neonates**
- **Co-Principal Investigator of ABLE Trial assessing age of blood in critically ill**
- **Received funding from Canadian Institutes of Health Research (CIHR) to conduct these studies**

Let's look at the evidence

- No shortage of bench and animal studies evaluating the RBC storage lesion
- Many studies consistently demonstrate changes affect survivability and function of RBCs
 - (biochemical, structural, enzymatic, morphological)
- I will **not** argue against this body of evidence
 - ie.
 - What effects are reversible post transfusion
 - What may be irreversible

But...

- Does this body of evidence translate into the ability of stored RBCs to affect oxygen delivery and uptake?
- To assess potential effects, we need to turn to clinical evidence
 - Observational and interventional studies

What do observational studies suggest?
A selective sample of the > 20 studies

Retrospective Trauma Studies.... Prolonged cell storage and adverse outcomes

- Increased **infections** after major trauma in 61 patients transfused with old blood
 - Association between old blood and the transfusion of aged blood (>14 days old) and increased length of ICU stay($p < 0.01$)⁽¹⁾ .
- Increased **length of stay** in 86 trauma victims with increased number of units **older than 14 days** ⁽²⁾
- Increased risk of **multiple organ failure** with transfusion of older blood⁽³⁾

(1) Offner et al, Arch Surg 2002

(2) Keller et al, J of Trauma, Injury and Critical Care

(3) Zallen et al, Am J Surg 1999

Retrospective Studies....

Prolonged cell storage and adverse outcomes

- In 698 ICU patients, association between the transfusion of aged blood (>14 days old) and increased length of ICU stay ($p < 0.01$)⁽¹⁾
- In severe sepsis, negative correlation ($r = -0.73, p < 0.01$) between age of RBC units transfused and survival ⁽²⁾
- In 416 CABG pts, adjusted increase of 1% in the risk of pneumonia per day of average increase in the length of storage of RBCs⁽³⁾

(1) Martin et al, Clin. Inv. Med

(2) Purdy et al, Can J Anesth, 1997

(3) Vamvakas et al, Transfusion 1999 and 2000

***More recent observational studies in
cardiac surgery patients***

Age of Transfused Red Cells and Early Outcomes After Cardiac Surgery

Cheng-Hon Yap, MBBS, MS, Lawrence Lau, MBBS, Mayur Krishnaswamy, MBBS, Mary Gaskell, BS, and Michael Yui, MBBS, MS

Departments of Cardiothoracic Surgery, Pathology (Blood Transfusion Laboratory), and Surgery, University of Melbourne, St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia

(Ann Thorac Surg 2008;86:554-9)

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– No association

The Association Between Duration of Storage of Transfused Red Blood Cells and Morbidity and Mortality After Reoperative Cardiac Surgery

Sukhjeewan Basran, MD

Robert J. Frumento, MS, MPH

Red blood cells (RBCs) undergo numerous changes during storage; however, the clinical relevance of these storage "lesions" is unclear. We hypothesized that the duration of storage of transfused RBCs is associated with mortality after repeat sternotomy for cardiac surgery, because these patients are at high risk for both RBC

(Anesth Analg 2006;103:15-20)

– Association

What are we to believe?

***Observational evidence to date
seems promising...***

But...

There are 2 issues with observational studies?

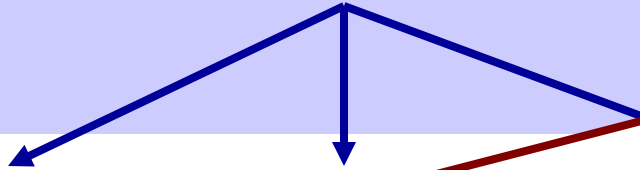
1. Defining “treatment” or “exposure”

- Average age?
- Median age?
- Oldest unit received?
- All are flawed

- Where is the cut-off?
 - For observational studies, a simple threshold (e.g. <14 days, > 14 days) is not sufficient
 - Need separation
 - Dose-response would be ideal

Defining treatment

Are these 3 patients the same?



Patient 1

Unit 1

Unit 2

Almost all of the retrospective studies suffered from this problem

| | | | | |
|---------|-----|----|------|----|
| Average | 7.4 | 22 | 12.6 | 23 |
| Median | 14 | 12 | 23 | 23 |
| Oldest | 19 | 22 | 23 | 23 |

ORIGINAL ARTICLE

Duration of Red-Cell Storage and Complications after Cardiac Surgery

Colleen Gorman Koch, M.D., Liang Li, Ph.D., Daniel I. Sessler, M.D.,
Priscilla Figueroa, M.D., Gerald A. Hoeltge, M.D., Tomislav Mihaljevic, M.D.,
and Eugene H. Blackstone, M.D.

- **6002 cardiac surgery patients**
- **Assessed whether prolonged RBC storage (>14 days) increased morbidity and mortality vs <14 days**
- **1 year mortality:**
 - 11% in “old”
 - 7.4% in “fresh”

Issues with Koch Study

- **Those that received older RBCs were much more likely to receive more than 6 units**
- **Greater morbidity in the >14 day group**
- **Analyzed mortality with a Kaplan-Meier statistic**
 - Does NOT adjust for important risk factors (units received, gender, morbidities)

The 2nd major problem with observational studies

- **2. Confounding by indication**
 - Sicker patients receive a greater number of transfusions
 - They also receive other interventions
 - In its simplest form, how can we compare patients that receive 1 unit versus >10 units
 - elaborate analysis cannot account for these differences
 - Apples and oranges
- Randomized clinical trials overcome these 2 biases
 - Investigator fixes treatment groups (fresh vs old/standard)
 - Known and unknown confounders are likely to be balanced

What does the clinical trial evidence suggest...

Randomized trials

Prolonged cell storage and adverse outcomes

Study design: Single centre RCT

Study Population: 17 trauma patients*

Intervention: Patients were allocated to shorter (<11 days) vs longer stored RBCs (>20 days)

Measurements: Mortality

Results: 4 deaths in short storage, 2 deaths in long storage

***Over 8000 admissions**

Randomized trials

Prolonged cell storage and adverse outcomes

Study design: Single centre RCT

Study Population: 22 mechanically ventilated patients who required at least 2 units of RBCs

Intervention: Patients were allocated to leukodepleted red cells that were stored for either < 5 days or > 20 days

Measurements: tissue oxygenation; CO₂ difference, pH_i

Results: No differences in Pg-PaCO₂, pH_i and oxygenation parameter

Randomized trials

Prolonged cell storage and adverse outcomes

Study Design: Multicentre RCT

Study population: 66 cardiac surgical and critically ill patients

Intervention: Fresh (< 8 days) vs standard blood bank issue RBCs

Results:

- 9 patients did not receive RBCs
- In 57 patients, median storage times in fresh was 4 days vs 19 days in standard group ($p < 0.0001$)
- ***Life-threatening complication or death in 27 % of fresh versus 13% of old ($p = 0.31$)***

Total Evidence from Randomized Trials

Total of 3 trials in critically ill adults

- 2 for feasibility**
- 1 surrogate measure**

Total patients evaluated: 57 + 17 + 22 = 96

Summary of RCT evidence

- Absolutely **no indication** that storage time has deleterious clinical consequences
- In fact, measures of mortality or serious morbidity seem to be going in the other direction in 2 of the trials
- Obviously, these trials were not powered to detect meaningful differences but it underscores the need for definitive trials

Additional issues

- **How do we define “fresh”?**
- **How do we balance the pressures of maintaining a healthy blood supply versus a small incremental risk?**
- **Can we extrapolate from a well-defined patient population to the entire population in need of a transfusion?**
 - (e.g. cardiac surgery, ICU, neonates)

In summary

- Without question, the storage lesion affects the quality of red cell product
- But, do these changes translate into clinical consequences given the current parameters/environment
 - (35-42 day outdate, testing, screening, leukoreduction etc.)
- Observational studies (largely retrospective)
 - suffer **fatal** flaws in defining treatment and confounding by indication
- Randomized clinical trials
 - too small and underpowered to evaluate or detect meaningful differences
- **Therefore, NO evidence that age of blood matters given the current standard outdate of 35-42 days**

Fear not, evidence is on the way

- **ARIPi (450 Canadian NICU patients)**
 - Fresh (≤ 7 days) vs standard of care
 - Enrolled 190 infants to date
- **ABLE (2500 Canadian adult ICU patients)**
 - Fresh (≤ 7 days) vs standard of care
 - Started enrollment last week
- **Red Cell Storage Age Study (1600 US Cardiac surgery patients)**
 - Fresh (≤ 10 days) vs “old” (>21 days)