The effect of blood donor characteristics on transfusion outcomes

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Funding

Canadian Blood Services
it's in you to give

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

CRCHUM
Université de Montréal
New studies show that young blood reverses the effects of aging when put into older mice

A blood-based protein that can rejuvenate the hearts of aging mice, has a similar effect on the mice’s brain and skeletal muscle function, according to scientists at Harvard University. (Photo by Tony Wyss-Coray.) (Reuters)
Young blood to be used in ultimate rejuvenation trial

20 August 2014 by Helen Thomson
Magazine issue 2983. Subscribe and save
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The doctor who survived Ebola Virus Disease because of blood transfusion.

(Photo: nbcnnews.com) The d
Objectives

• Understand how blood donor characteristics may be related to adverse events after RBC transfusion;
• Present a framework to study the blood donor-recipient continuum;
• Present results from a Canadian transfusion cohort study using large data
  – Effect of donor age and sex on RBC transfusion survival
Why study blood... again?
After all... has been in use for a long time now!
Why study blood

• Highly used therapy
  – Most common medical intervention
  – More than 100 million RBC transfusions a year worldwide
Why study blood

• Costly
  – In 2012 in Canada, for transfusable products
    • 850 million dollars
    • Excludes
      – Cost to transfuse the product (hospital, nurse, etc.)
      – Cost associated with complications

TRANSFUSION 2004;44:1479-1486.
Lack of evidence of efficacy in anemic patients despite good physiological rationale

Review Article

Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature*

Paul E. Marik, MD, FACP, FCCM, FCCP; Howard L. Corwin, MD, FACP, FCCM, FCCP
Lack of evidence of efficacy in anemic patients despite good physiological rationale

- Mortality
Lack of evidence of efficacy in anemic patients despite good physiological rationale

- Infections

Figure 3. Association between blood transfusion and the risk of infectious complications (odds ratio [OR] and 95% confidence interval [CI]). ICU, intensive care unit.
Lack of evidence of efficacy in anemic patients despite good physiological rationale

- ARDS

Figure 4. Association between blood transfusion and the risk of developing adult respiratory distress syndrome (odds ratio [OR] and 95% confidence interval [CI]). ICU, intensive care unit.
Why?

• Are there harms that offset potential benefits?
  – Transfusion reactions?
    • Lethal ones are rare…
  – Transfusion associated/related infections?
  – Transfusion associated circulatory overload?
  – Transfusion related acute lung injury?
Why

- Transfusion Related Immunomodulation
  - Increased risk of infection
  - Accelerated cancer growth
  - Organ dysfunction
  - Cause unknown, but persist even with leukoreduced products
Targets for the study of transfusion

- **Donor**
  - Appropriate selection
  - Appropriate supply

- **Manufacture**
  - Transformation (buffy coat, leukoreduction, preservatives…)
  - Screening (infections)

- **Storage**
  - Duration
  - Technology…

- **Administration**
  - Correct indication
  - Correct dose
  - To the good patient…
Study the donor
Why study the donor

• “Proven” efficacy for infectious disease
Why study the donor

• Age of donor
  – Aging affects
    • Erythropoiesis
    • Increased DNA damage
    • Modified cellular function
      – Oncogenicity
    • Change in cell membrane
    • Increased amount of cytokines in blood
      – TNF-α
  – Age has been shown to affect outcome in organ transplantation
    • Stem cell: RR 1.10, 95% CI 1.06-1.14 per decade
      – Memory T-cells (more memory = more GVHD)
Effect of Blood Donor Characteristics on Transfusion Outcomes: A Systematic Review and Meta-Analysis

Michaël Chassé, Lauralyn McIntyre, Shane W. English, Alan Tinmouth, Greg Knoll, Dianna Wolfe, Kumanan Wilson, Nadine Shehata, Alan Forster, Carl van Walraven, Dean A. Fergusson

Hospital mortality

<table>
<thead>
<tr>
<th>Mean donor age</th>
<th>1</th>
<th>Mean Difference (IV. Random, 95% CI)</th>
<th>-6.62 [-9.92, 0.64]</th>
<th>Null, favours older donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum donor age</td>
<td>1</td>
<td>Mean Difference (IV. Random, 95% CI)</td>
<td>-6.24 [-12.43, -0.05]</td>
<td>Favours older donor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [Age]</th>
<th>SD [Age]</th>
<th>Total</th>
<th>Mean [Age]</th>
<th>SD [Age]</th>
<th>Total</th>
<th>Mean Difference IV, Random, 95% CI (Age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean donor age</td>
<td>40.95</td>
<td>9.54</td>
<td>19</td>
<td>45.99</td>
<td>10.03</td>
<td>41</td>
<td>-6.64 [-9.92, 0.64]</td>
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<tr>
<td>Maximum donor age</td>
<td>45.37</td>
<td>11.42</td>
<td>19</td>
<td>51.61</td>
<td>11.3</td>
<td>41</td>
<td>-6.24 [-12.43, -0.05]</td>
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</tbody>
</table>

All recipients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
<th>1.60 [0.96, 2.67]</th>
<th>Null, favours no sex mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>All recipients</td>
<td>0.47</td>
<td>0.2606</td>
<td>1.60 [0.96, 2.67]</td>
<td>1.60 [0.96, 2.67]</td>
<td>Null, favours no sex mismatch</td>
</tr>
<tr>
<td>Female recipients</td>
<td>0.1823</td>
<td>0.3934</td>
<td>1.20 [0.56, 2.59]</td>
<td>1.20 [0.56, 2.59]</td>
<td></td>
</tr>
<tr>
<td>Male recipients</td>
<td>0.8755</td>
<td>0.398</td>
<td>2.40 [1.10, 5.24]</td>
<td>2.40 [1.10, 5.24]</td>
<td></td>
</tr>
</tbody>
</table>
Why study donor

- **Sex**
  - Different enzymatic activity in RBC between sex
    - Effect of sex-mismatched transfusions?
  - Blood composition
    - Anti-neutrophils and others
Methods

- **Design:** Retrospective longitudinal cohort study (quasi-randomized!)
- **Population:**
  - Any patient
  - At least one allogenic RBC transfusion
  - In the included centers (The Ottawa Hospital – General Campus, The Ottawa Hospital – Civic Campus, The University of Ottawa Heart Institute, and The Ottawa Hospital – Riverside Campus)
- **Source of data**
  - Canadian Blood Services (Donor data)
  - The Ottawa Hospital DataWarehouse (transfusion data, culture results, lab results)
  - ICES (Registered Person Database, Ontario Cancer Registry, CIHI-DAD)
The framework

Donor

Canadian Blood Services

Hospital Datawarehouse

Data analysis

Patient

Institute of clinical evaluative sciences of Ontario
Proposed Framework

- **Timeframe**
  - October 2006 to December 2013
Analysis plan

• Main analysis
  – Extended cox model
    • Multiple transfusions
    • Over time
    • From multiple donors
    • Each unit having different characteristics
    • Adjustment for confounding
  – Main exposures: Donor Age, Donor sex
  – Main outcome: Survival
## Analysis

### Table

<table>
<thead>
<tr>
<th>ID</th>
<th>Start</th>
<th>End</th>
<th>Cum M</th>
<th>Cum F</th>
<th>Total</th>
<th>Cov1</th>
<th>Censor</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>A</td>
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<td>0</td>
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<td>2</td>
<td>A</td>
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<tr>
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<td>100</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>75</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
Confounding

Blood supply organization

Blood donation

Blood preparation and attribution of a de-identified unique number

Transport to hospital

Blood is randomly selected among compatible blood units

Hospital

Medical personnel orders a blood transfusion

Donor characteristics are randomly distributed among recipients

Blood is transfused to the recipient.

Images used to create this figure are a courtesy of Sura Nualpradid, photostock, cooldesign, Moggara, Praisaeng and Stuart Miles / FreeDigitalPhotos.net
Original Investigation

Association of Blood Donor Age and Sex With Recipient Survival After Red Blood Cell Transfusion

Michaël Chassé, MD, PhD, FRCPC; Alan Tinmouth, MD, MSc, FRCPC; Shane W. English, MD, MSc, FRCPC;
Jason P. Acker, MBA, PhD; Kumanan Wilson, MD, FRCPC; Greg Knoll, MD, MSc, FRCPC;
Nadine Shehata, MD, MSc, FRCPC; Carl van Walraven, MD, MSc, FRCPC; Alan J. Forster, MD, MSc, FRCPC;
Timothy Ramsay, PhD; Lauralyn A. McIntyre, MD, MSc, FRCPC; Dean A. Fergusson, MHA, PhD
Figure 1. Flowchart of the Study Cohort

- 32798 Eligible recipients
  - 2279 No valid OHIP number
    - 30519 Valid OHIP number
      - 16 Invalid linkage
        - 30503 Eligible recipients
          - 80755 Included donors
            - 187960 Eligible units
Main results

Table 3. Unadjusted and Adjusted Patient Survival According to Donor Age and Sex, per Additional Unit Transfused

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-19.9</td>
<td>1.14 (1.12-1.16)</td>
<td>1.08 (1.06-1.10)</td>
</tr>
<tr>
<td>20-29.9</td>
<td>1.06 (1.04-1.08)</td>
<td>1.06 (1.04-1.09)</td>
</tr>
<tr>
<td>30-39.9</td>
<td>1.01 (0.99-1.03)</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>40-49.9</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>50-59.9</td>
<td>1.00 (0.99-1.02)</td>
<td>1.01 (0.99-1.02)</td>
</tr>
<tr>
<td>60-69.9</td>
<td>1.02 (1.00-1.03)</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>≥70.0</td>
<td>0.89 (0.83-0.95)</td>
<td>0.96 (0.89-1.03)</td>
</tr>
<tr>
<td>Donor sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Female</td>
<td>1.08 (1.07-1.09)</td>
<td>1.08 (1.06-1.09)</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

<sup>a</sup> Adjusted for recipient age, recipient sex, and Charlson Comorbidity Index.
Interpretation

• Reduced survival after RBC transfusion from:
  – Female donors
  – Young donors

• Deserves confirmation:
  – ARR 6.2% per year; 95% CI 5.4% to 7.0% at mean 6 transfusions
  – Number Needed to Treat (NNT): 16
Limitations

• Not evidence that young age or donor sex is causal in the survival pathway of transfusion recipients
  – Exact mechanisms unknown
  – Anything that is associated with donor age or donor sex could be responsible for the observed change in survival

• Risk of unmeasured confounders
  – But likely limited (quasi-random allocation, blinding…)

• Effect not homogeneous across subgroups

• Dose-response relationship but effect not linear
Next steps

• Additional exposures
  – Blood group (ongoing) ?
  – Manufacture (ongoing) ?
  – Novel infections?
  – Donor biomarkers?

• Additional linkages?
  – Potential for mechanistic studies?
    • Linkage with biobanks?

• Additional outcomes
  – Cancer (ongoing) ?
  – Infections (ongoing) ?
  – MI (ongoing) ?
  – Renal failure (ongoing)
Confirmatory trial

Application Details

Funding Opportunity:
Project Grant: Fall 2016 (2016-10-20)

Research Proposal
An innovative Trial Assessing Donor Sex on Recipient Mortality (iTADS)

Chassé, Fergusson
Conclusion

- Donor characteristics probably affect transfusion outcome
  - Including long-term
- Donor sex and donor age seem to be important factors
- Confirmatory studies ongoing
Acknowledgements

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