Red Cell Transfusion

We’re too liberal

Canada Critical Care Forum
October 26, 2015

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Anemia is part of critical illness

- 95% anemic by 3rd day in ICU
- 45% will be receive RBC transfusion in the ICU

Figure 1. Course of Hemoglobin (Hb) Patterns by Admitting Hb Level Category

Corwin H, et. al. CCM 2004
Rate of RBC vary among Canadian ICUs

Hutton B, et al. CJA 2005
Why do we want to transfuse anemic patients?

• Because we assume anemia to be injurious?

• To increase oxygen delivery to tissues/organs?

• Because low hemoglobin is an abnormal value?
TRICC trial
Transfusion Requirements in Critical Care (Adults)

Study design: Multicentre RCT
Setting: 25 ICUs;
Study Period: 1994-1997
Intervention: 70 g/L vs 100 g/L hemoglobin trigger
Outcomes: 30 day all-cause mortality and organ failure

Hebert PC, et al. NEJM 1999
TRICC trial
Transfusion Requirements in Critical Care (Adults)

Bottom line: Restrictive as good or better

Blood saved in restrictive arm:
- 1 unit RBC/pt saved
- 33% vs. 0% of patients were NOT transfused

Hebert PC, et al. NEJM 1999
Transfusion strategies in *pediatric ICU*
70 vs 95 g/L; n = 637 patients

**Bottom line:** No difference in new or progressive MODs (or mortality)

**Blood saved in restrictive arm:**
- 44% fewer transfusions
- 52% vs. 2% of patients were NOT transfused
Transfusion in hip surgery in patients with risk factors for CVD (FOCUS trial)
80 vs 100 g/L; n = 2016 patients

Bottom line:
• No difference in death or ability to walk without assistance
• No difference in ACS

Blood saved in restrictive arm:
• Median transfused units 2 vs 0
• 59% vs. 3% of patients were NOT transfused

Carson JL, et al. NEJM 2011
Transfusion in acute severe GI hemorrhage 70 vs 90 g/L, n = 2372 patients

Bottom line
- Lower mortality in restrictive group (5% vs 9%)

Villanueva, et al. NEJM 2013
Transfusion in acute severe GI hemorrhage
70 vs 90 g/L, n = 2372 patients

Blood saved in restrictive arm:
- > 1 unit RBC/pt saved
- 51% vs. 14% of patients were NOT transfused
- Decreased bleeding in restrictive group!

Villanueva, et al. NEJM 2013
Transfusion in septic shock
70 vs 90 g/L, n = 998 patients

Bottom line:
• No difference in mortality or adverse events

Blood saved in restrictive arm:
• Median units transfused: 1 vs 4
• 36% vs. 1% of patients were NOT transfused

Holst, et al. NEJM 2014
Transfusion as part of resuscitation protocols

- ProCESS (n = 1341)

- ARISE (n = 1600)

Transfusion trigger of HCT 30% (HgG ~ 90 g/L) based on venous saturation

- NO benefit to transfusion in either of these trials
- TWICE as much blood transfused in EDGT arms

ProCESS investigators. NEJM 2014
ARISE investigators. NEJM. 2014
Transfusion requirements after cardiac surgery (TRACS)
Mean HbG: 91 vs 105 g/L, n = 502 patients

Bottom line
• NO difference in mortality or major morbidity (11 vs. 10%)

Blood saved in restrictive arm:
• 53% vs. 22% of patients were NOT transfused
How has research impacted survival?

Glucose Control: Meta-analysis (CMAJ 2009;180:821)

RBC trigger RCTs - in cardiac surgery

Bottom line
- NO clear differences in mortality

Curley, et al. CCM 2014
Is there a population that may benefit from a high hemoglobin trigger?

Nakamura et al

A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery

Rosana Ely Nakamura, MD, Jean-Louis Vincent, PhD, Julia Tizue Fukushima, MSc

• Subgroup analysis of TRACS study
• No difference in the primary outcome or mortality, or acute kidney injury, or ARDS…but less cardiogenic shock

Is there a population that may benefit from a high hemoglobin trigger?

Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease

Jeffrey L. Carson, MD, a Maria Mori Brooks, PhD, b J. Dawn Abbott, MD, c Bernard Chaitman, MD, d

- Pilot RCT. N = 110. 80 vs. 100 g/L
- Major baseline imbalance in age (67 vs. 74 years)
- Primary outcome (death, MI, revascularization)
  - Liberal: 6 patients (10.9%)
  - Restrictive: 14 patients (25.5%)

Is there a population that may benefit from a high hemoglobin trigger?

Transfusion Requirements in Surgical Oncology Patients

A Prospective, Randomized Controlled Trial

Juliano Pinheiro de Almeida, M.D., Jean-Louis Vincent, M.D., Ph.D.,

- Single centre study; Sao Paulo, Brazil
- N = 198.  70 vs. 90 g/L
- Major abdominal oncology surgery requiring ICU admission
- Primary outcome – composite of mortality and morbidity
  - Liberal: 19 patients (20%)
  - Restrictive: 36 patients (36%)

Pinheiro de Almeida, et al. Anesthesiology. 2015
Is there a population that may benefit from a high hemoglobin trigger?

Neurocritical care

- Predictably poor outcomes in more severe anemia
- Abnormal tissue oxygenation associated with poor outcome

- Concerning focus on surrogate markers of oxygenation
  - Surrogates ≠ valid correlate
  - Contribution to causal pathway of poor outcome is unknown
  - Ability to predict the outcome of interest is unknown
What’s wrong with the current evidence base?

- Studies have failed to consider the ‘cause’ of anemia

- Hypothesis has been one sided
  - That is, all anemia assumed to be injurious

- Founded on universal triggers instead of individual patient characteristics or measured ‘consequences’ of anemia
What’s wrong with the current evidence base? Considering the cause of anemia?

- Blood loss (acute vs. chronic; iatrogenic vs. trauma or surgical, gastritis)?
- Contribution of renal disease?
- **Anemia of inflammation?**
- Nutritional deficiency?
- Destruction?
- Marrow failure?
What’s wrong with the current evidence base?

Is all anemia injurious?

Association with poor prognosis ≠ causation

- Reflects severity of illness
- Looses prognostic significance when severity of illness or inflammation is considered
What’s wrong with the current evidence base
We are designed to adapt!

How much oxygen is enough in critical illness

Hebert PC, et al. CMAJ. 1997
What’s wrong with the current evidence base
Is all anemia injurious?

Anemia is a genetically programmed response to illness

Zarychanski, et al. CMAJ. 2008
What’s wrong with the current evidence base
Could anemia be protective?

Two potential mechanisms:

• Iron sequestration
  – Suppression of Fenton reaction: $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^\bullet + \text{OH}^-$
  – Inhibition of bacterial growth

• Decreased viscosity
  – Increased capillary flow
  – Decreased cardiac work

Zarychanski, et al. CMAJ. 2008
Iron deficiency, even mild anemia, may protect against malaria, TB and cancer
Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial

Sunil Sazawal, PhD, Prof Robert E Black, MD, Mahdi Ramsan, MD, Hababu M Chwaya, Rebecca J Stoltzfus, PhD, Arup Dutta, BCA, Usha Dhingra, MCA, Ibrahim Kabole, MD, Saikat Deb, PhD, Mashavi K Othman, MD, Fatma M Kabole

- 24,076 children in Tanzania
- 12% increase in death
- 11% increase in hospitalization
What’s wrong with the current evidence base
We’re too trigger happy!

• Transfusion is more complicated than a single number

• When will a patient be harmed by the anemia?

• Which patients will benefit from a transfusion?
In summary

• The available evidence demonstrates the safety of mild to moderate anemia is a diverse selection of patients

  • Safe
  • Preserves a scare and expensive donor resource
  • Reduces known harms (e.g. transfusion transmitted infections)
In summary

• Further research should consider:
  • Reasons for anemia
  • Characteristics that predict when a patient may benefit from transfusion
    • Coronary disease?
    • Neurocritical care?
    • Age?
Outcomes should be clinically relevant and patient-centered
For every complex problem, there is a solution that is simple, neat, and wrong.

(H. L. Mencken)