CLINICAL ADVERSE EFFECTS OF RBC TRANSFUSIONS: REMAINING ISSUES RELATED TO STORAGE?

Morris A. Blajchman, MD, FRCP(C)
Emeritus Professor, McMaster University
Hamilton, Ontario, CANADA

RBC TRANSFUSIONS: GENERAL PRINCIPLES

- RBCs are usually dispensed on a first-in, first-out basis.
- Storage is limited to 42 days in most jurisdictions, based on in-vivo RBC recovery and survival after transfusion.
- During storage at 4°C, RBCs degrade slowly but this degradation is not thought to be harmful to the recipient.
- Until recently, fresh RBCs (stored for 1 week or less) were indicated in only select clinical situations. (i.e., neonatal and cardiac surgery patients.)
- Is there an in-vitro difference between “fresh” and “old” blood?
- Is there positive clinical relevance to the recipient receiving “fresh” rather than “old” RBCs?

IN-VITRO EFFECTS OF RBC STORAGE - 1

- Well characterized structural, biochemical, metabolic, inflammatory, and physiological changes occur during RBC storage. Although the *in-vitro* "storage lesions" have been quite well characterized, their clinical relevance has remained relatively elusive.
- Hemolysis < 1% at 42 days.
- Progressive decrease in intracellular 2, 3-DPG and ATP.
- Increased accumulation of extracellular free Hbg both extracellularly and contained within RBC micro-vesicles.

IN-VITRO EFFECTS OF RBC STORAGE - 2

- Changes to RBC membrane proteins which are associated with reduced deformability.
- Progressive accumulation of potassium ions.
- Accumulation of multiple biologic substances including cytokines, etc. Enzymes which theoretically can cause in vivo biological effects including inflammation and immunomodulation in a recipient.

Zimrin AB and Hess JR Vox Sanguinis 2009; 96: 93-103.

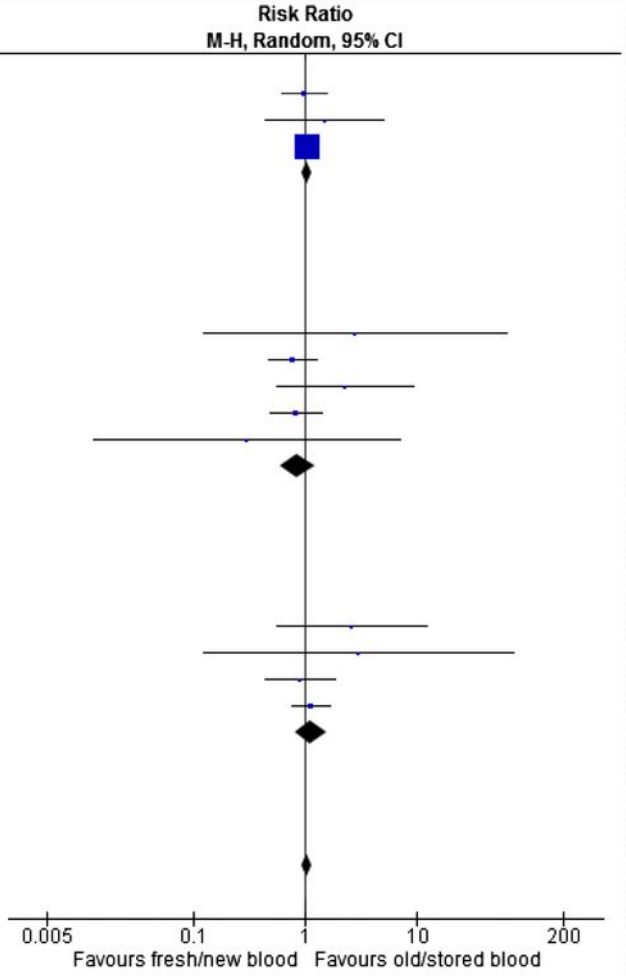
REPORTED IN-VIVO EFFECTS OF STORED RBCs

- Most such effects were reported from retrospective observational studies ranging in size from 61 to 364,037 subjects.
- Includes cardiac surgery (14), trauma (14), critical care (16), or oncologic (16) patients. (n=60)
- Reported clinical effects include increased mortality, sepsis or other bacterial infections, length of hospital stay, occurrence of venous thrombosis, and multi-organ failure.
- Most of these studies (>70%) show no clinical differences between those subjects who received "fresh" versus "old" RBC transfusions.
- Many of these studies suggest better clinical outcomes in those patients who received "fresh" RBCs.

Reference: Qu L and Truilzi DJ Cancer Control 2015; 22: 26-37

Fresh vs older blood outcome mortality by specific duration of follow-up.

Study or Subgroup	Fresh blood Events	Total	Older/standard/blood Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 90-day mortality (longer)						
Fergusson et al. 2012	30	188	31	189	4.2%	0.97 [0.61, 1.54]
Hebert et al. 2005	5	26	4	31	0.6%	1.49 [0.45, 4.98]
Lacroix et al. 2015	448	1211	430	1219	79.8%	1.05 [0.94, 1.17]
Subtotal (95% CI)		**1425**		**1439**	**84.6%**	**1.05 [0.95, 1.16]**
Total events	483		465			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.38)						
1.18.2 28/30-day mortality						
Bennett-Guerrero et al. 2009	1	12	0	11	0.1%	2.77 [0.12, 61.65]
Kor et al. 2012	17	50	22	50	3.6%	0.77 [0.47, 1.27]
Schulman et al. 2002	4	8	2	9	0.5%	2.25 [0.55, 9.17]
Steiner et al. 2015	23	538	29	560	3.1%	0.83 [0.48, 1.41]
Strauss et al. 1996	0	21	1	19	0.1%	0.30 [0.01, 7.02]
Subtotal (95% CI)		**629**		**649**	**7.4%**	**0.85 [0.60, 1.21]**
Total events	45		54			
Heterogeneity: Tau² = 0.00; Chi² = 2.97, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.18.3 In-hospital mortality						
Aubron et al. 2012	5	25	2	26	0.4%	2.60 [0.55, 12.19]
Dhabangi et al. 2013	1	37	0	37	0.1%	3.00 [0.13, 71.34]
Fernandes da Cunha et al. 2005	9	26	10	26	1.7%	0.90 [0.44, 1.85]
Heddle et al. 2012	35	309	61	601	5.8%	1.12 [0.75, 1.65]
Subtotal (95% CI)		**397**		**690**	**8.0%**	**1.12 [0.80, 1.56]**
Total events	50		73			
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**2451**		**2778**	**100.0%**	**1.04 [0.94, 1.14]**
Total events	578		592			
Heterogeneity: Tau² = 0.00; Chi² = 6.73, df = 11 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² = 0%						



From: Alexander PE et al Blood 2016; 127: 400-410

DATA FROM 12 PUBLISHED RCTs: A META-ANALYSIS - 1

- The 12 trials recruited 5,229 subjects.
- The subject size in the 12 trials ranged from 17 to 2,430.
- Six studies were feasibility (pilot) studies intending to inform on the potential conduct of larger studies.
- 2,451 subjects were assigned to the “fresh” arm and 2,778 to the “older” RBC or “standard” arm.
- Allogeneic blood was used exclusively in 11 of the 12 studies; one study did not specify type of blood used.

Alexander PE et al Blood 2016; 127: 400-10

DATA FROM 12 PUBLISHED RCTs: A META-ANALYSIS - 2

- Outcomes measured included mortality, adverse events, and nosocomial infections which were similar in both arms.
- Mortality: RR 1.04; (CI 0.94 – 1.14) (not significant)
- Adverse Events: RR 1.02; (CI 0.91 – 1.14) (not significant)
- Infections: RR 1.09; (CI 1.00 – 1.18) P = 0.04
  (probably due to patient heterogeneity.)
- Subgroup analyses were not reported because the heterogeneity that was observed probably occurred by chance.

Alexander PE et al Blood 2016; 127: 400-10

DATA FROM 6 LARGER RCTs

- Steiner ME et al. NEJM 2015; 372: 1419-1429. (1098 cardiac surgery patients)
- Lacroix J et al. NEJM 2015; 372: 1410-1418. (878 critically ill adults)
- Fernandes da Cunha DH et al. Transfus Med 2005; 15-467-473 (52 VLBW neonates)
- Kor DJ et al. Am J Respir Crit Care Med 2012; 185: 842-850 (100 ICU patients)
- Strauss RG et al. Transfusion 1996; 36: 873-878 (40 VLBW neonates)
- Fergusson DA et al. JAMA 2012; 308: 1443-1451 (377 VLBW neonates)

THE ARIPI RANDOMIZED TRIAL-1 IN VLBW NEONATES (JAMA 2012)

- Double-blind RCT in 377 premature VLBW (<1250 g) infants.
- Subjects in 6 tertiary NICUs were randomly assigned to receive RBCs either stored for 7 days or less (n=188) or standard issue RBCs (n=189).
- The primary outcome was a composite measure of major neonatal morbidities including: necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, IVH, or death.

THE ARIPI RANDOMIZED TRIAL-2 IN VLBW NEONATES (JAMA 2012)

- The mean age of RBCs was 5.1 (SD, 2.0) vs 14.5 (SD, 8.3) days in the 2 arms.
- For neonates in the fresh arm 52.7% versus 52.9% in the standard arm experienced the primary outcome. Also, no difference in the rate of clinically suspected infection was observed.
- CONCLUSION:

  The use of fresh RBCs compared to the use of standard practice RBCs use did not improve the outcome of VLBW neonates requiring an RBC transfusion.

Fergusson D et al JAMA 2012, 308: 1443-51.

THE RECESS TRIAL IN CARDIAC SURGERY PATIENTS (NJEM 2015)

- RCT (2 arms) in patients undergoing complex cardiac surgery (age 12 or greater) that were also likely to undergo RBC transfusions (33 hospital sites in the US).
- Subjects were randomly assigned to receive < 10 day stored RBCs (n=538) or > 21 day-stored RBCs (n=560).
- Primary outcome was the change in the Multiple Organ Dysfunction Score (Δ MODS); (range 0-24) from the preoperative state to the highest Δ MODS through day 7, or time of death.
- In 1098 subjects the Δ MODS was 8.5 and 8.7 in the two arms (CI for the difference was -0.6 to 0.3). (P=0.44).
- The 28 day mortality was 4.4% and 5.3% (P=0.57).

Steiner ME et al NEJM 2015; 372: 1419-29.

THE ABLE TRIAL IN ICU PATIENTS

- RCT in critically ill adults. 1,211 subjects received fresh RBCs (6.1 ± 4.9 days) and 1,219 standard-issue RBCs (22.0 ± 8.4 days).
- The primary outcome was 90-day mortality which occurred in 37.0% in the fresh RBC arm (n=448) and 35.3% in the standard issue RBC arm (n=430) (95% CI; -2.1 to 5.5)
- No significant difference in any of the secondary outcomes (major illness; duration of respiratory, hemodynamic, or renal support; LOS in hospital; or transfusion reaction rate).
- Study included 64 hospitals: in Canada (n=26), UK (n=20), France (n=10), the Netherlands (n=7), and Belgium (n=1).

Lacroix J et al NEJM 2015; 372: 1410-1418.

Kaplan–Meier Survival Analysis of Time to Death in the Intention-to-Treat Population.

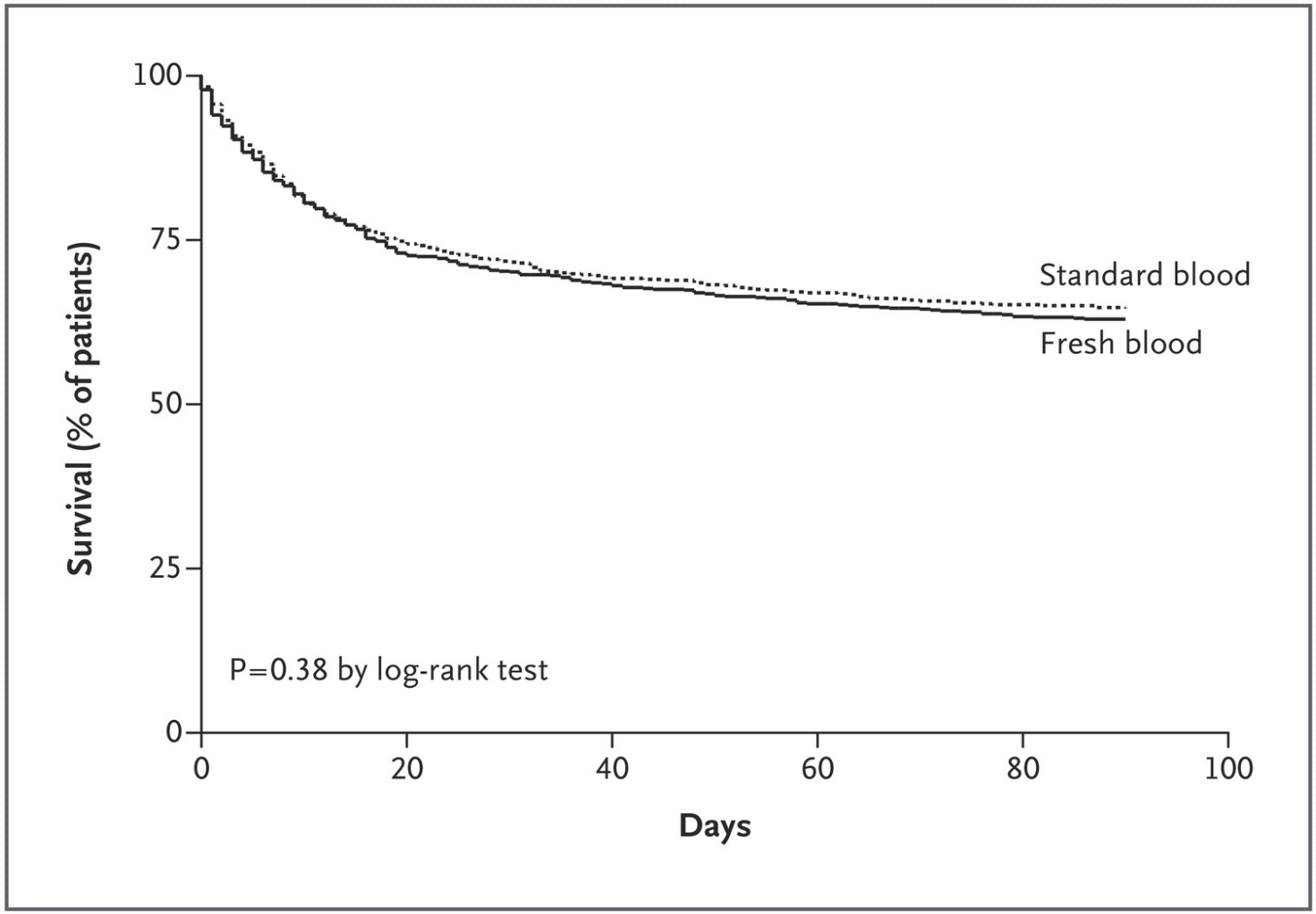


Figure 2. Kaplan–Meier Survival Analysis of Time to Death in the Intention-to-Treat Population.
The intention-to-treat population included 2430 patients. The hazard ratio in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2).

Lacroix J et al. N Engl J Med 2015;372:1410-1418.

CONCLUSIONS AND UNANSWERED QUESTIONS

- The available RCT data indicate no support for changing RBC transfusion practice toward the use of fresher RBCs.
- Concern however remains about subjects who received RBCs stored for 35 days or more especially sicker and elderly patients.
- There is also some concern about the possible adverse effect of transfusing “fresh” RBCs.
- Use of stored blood in specific clinical situations (i.e., subjects with severe anemia) remains a concern.

THE "TOTAL" RCT IN CHILDREN WITH SEVERE ANEMIA AND ELEVATED LACTATE LEVELS

- A non-inferiority RCT including 290 children, aged 6-60 months) done in Kampala, Uganda (Hgb 5g/dL or lower and a lactate level of 5 mmol/L or higher).
- Subjects were assigned to 2 RBC arms (fresher 1-10 day RBC storage – n=145, or longer 25-35 day storage – n=145).
- Mean presenting hemoglobin was 3.7 g/dL (SD 1.3) and mean lactate level was 9.3 mmol/L (SD 3.4).
- Clinical assessment, cerebral oxygen saturation, adverse events, survival and 30-day recovery was not different between the 2 arms.
- CONCLUSION: Among hypoxic children with lactic acidosis due to severe anemia, the transfusion of longer-storage (mean 32 days) versus shorter-storage (mean 8 days) RBCs did not result in an inferior reduction of the elevated lactate levels.

Dhabangi A et al JAMA 2015; 314: 2514-23.

RBCs STORED FOR MORE THAN 35 DAYS IN HIGH RISK PATIENTS - 1

- Goel et al performed a retrospective observational study in 28,247 transfused patients given 129,483 RBC units of different storage ages.

- Compared morbidity, mortality and LOS in patients transfused exclusively with <21-day, >28-day, and >35 day RBC storage.

- Morbidity >35-day storage: adj OR 1.19 (95% CI 1.07-1.32) p=0.002.
  Morbidity >28-day storage: adj OR 1.06 (95% CI 0.97-1.15) p=0.2.

Goel R et al Transfusion 2016; in press

RBCs STORED FOR MORE THAN 35 DAYS IN HIGH RISK PATIENTS - 2

- Neither >35-day nor >28-day RBC storage was associated with increased mortality.
- LOS was increased for both >28-day and >35-day RBCs for all patients as well as the critically ill and older subgroups..
- The use of 35-day RBCs were associated with increased morbidity (adj OR 1.25; p=0.002) and mortality (adj OR 1.38; p=0.009) in critically ill patients.

AUTHOR'S CONCLUSIONS

1. The clinical implications are that consideration be given as to whether blood units should be triaged to avoid giving the very oldest blood to the sickest and/or oldest patients.

2. Efforts should be made to reduce RBC transfusion requirements in the sickest and oldest patients and to avoid the transfusion of older units.

3. RBCs transfused in the last 7 days of their 42-day storage *may* be associated with adverse outcomes in high risk patients.

FURTHER THOUGHTS

- The study by Goel et al is a well done observational retrospective study.

- In my view, however, the conclusions need to be carefully re-examined in well-designed and adequately powered RCTs!

RCTs ARE THE GOLD STANDARD TYPE OF STUDY FOR THE DECISION-MAKING OF CLINCIAL EVIDENCE - 1

- I have personally been directly involved in the following large RCTs:

1. TRICC - Hebert P NEJM 1999 (critically ill adults)
2. ARIPI - Fergusson D JAMA 2012 (VLBW neonates)
3. ABLE - Lacroix J NEJM 2015 (critically ill adults)
4. RECESS - Steiner M NEJM 2015 (cardiac surgery subjects)

RCTs ARE THE GOLD STANDARD TYPE OF STUDY FOR THE DECISION-MAKING OF CLINCIAL EVIDENCE - 2

- The TRICC RCT indicated that the volume of blood transfused was associated with increased risk of morbidity and mortality in RBC recipients.
- The ARIPI, ABLE and RECESS studies all indicated that the transfusion of longer storage RBCs does not increase the incidence of morbidity and mortality compared to that seen with recipients of fresher RBCs.
- However the two extremes of the RBC storage period were not adequately examined in any of these studies.
- The latter needs to be further examined in adequately powered RCTs.

CLINICAL ADVERSE EFFECTS OF RBC TRANSFUSIONS: REMAINING ISSUES?

Thank you for your attention and for awarding me the BBTS Blundell Award.