The Transfusion Requirements in Cardiac Surgery (TRICS-III) trial–An evaluation of restrictive versus liberal red cell transfusion strategy

Definition of the appropriate red cell transfusion thresholds has been a controversial and highly debated topic for years. Numerous studies and controlled trials have investigated liberal versus restrictive transfusion strategies in very specific critically ill patient populations:

- Transfusion Requirements in Critical Care (TRICC)–Published in 1999, investigated a liberal versus restrictive transfusion strategy in ICU patients and demonstrated slightly lower 30-day mortality in the restrictive patient group.
- A subset analysis of the TRICC trial–Published in 2001, evaluated patients with or at risk of cardiovascular disease, and found no significant differences in 30 or 60-day mortality between the two transfused groups.
- A study in patients with moderate to severe head injuries–Published in 2006, revealed no difference in 30-day mortality rates between the liberal versus restrictive patients.
- Transfusion Strategies for Patients in Pediatric Intensive Care Units (TRIPICU)–Published in 2007, demonstrated no significant differences in rates of mortality between the two groups.
- Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)–Published in 2011, showed no significant difference in hospital or 60-day mortality between the two transfusion strategies.
- Transfusion Strategies for Acute Upper Gastrointestinal Bleeding–Published in 2013, found lower mortality with a restrictive transfusion strategy.
- Transfusion Requirements in Septic Shock (TRISS)–Published in 2014, investigated liberal versus restrictive transfusion strategy in patients with septic shock and found no significant difference in 90 day mortality.
- Two meta analyses – Published in 2014, found that a restrictive transfusion strategy was associated

In the news

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with reduced mortality, cardiac events, re-bleeding and bacterial infections.

In one of the more recent studies, Transfusion Requirements in Cardiac Surgery (TRICS-III), investigators assessed the effects of restrictive versus liberal transfusion strategy among over 5000 cardiac surgery patients 18 years and older at 73 sites in 19 countries. Hemoglobin levels were measured before, during and after surgery at defined intervals and, when below the transfusion trigger, one unit of packed red blood cells was transfused and hemoglobin levels were reassessed. The transfusion trigger for the restrictive group was a hemoglobin concentration of less than 7.5 g/dL, and for the liberal group less than 9.5 g/dL during surgery or afterwards while in ICU and less than 8.5 g/dL in non-ICU locations.

Overall results for the restrictive transfusion group were similar to the liberal transfusion group for death and major disability (11.4% vs. 12.5%), however the restrictive strategy was associated with lower risk among elderly patients (>75 years). In addition, the restrictive transfusion strategy group required significantly fewer red blood cells than the liberal group (52.3% vs. 72.6%). This trial provides evidence that restrictive transfusion protocols are not harmful to cardiac surgery patients and these patients can be safely managed with hemoglobin thresholds as low as 7.5 g/dL.


Is age just a number? A review of recent RBC storage age studies

For years many of the known risks of blood transfusion were associated with infectious disease transmission and transfusion reactions. Recently, there has been much discussion and study of the risks associated with the storage lesion, biochemical changes that occur in RBCs during storage. The damage caused by refrigeration does lead to in vivo hemolysis of some of the transfused red cells. The amount of hemolysis increases with increased length of storage, but is not clinically significant in donations from healthy volunteers. Five major randomized, controlled clinical trials looked at the impact of short vs. long length of storage on clinical outcomes in various patient populations.

The aim of the Age of Red Blood Cells in Premature Infants (ARIPI) trial was to discover if transfusions of RBCs stored for seven days or less were associated with lower risk of major nosocomial infections and organ dysfunction in neonatal ICU patients, specifically premature, very low birth weight infants. The conclusion was that transfusion of these ≤ 7-day old RBCs did not improve outcomes in this patient population when compared to the standard of care (RBCs stored on average 14.6 days prior to transfusion).

The Age of Blood Evaluation (ABLE) trial compared transfusion of RBCs stored for ≤ 7 days with standard-issue RBCs in critically ill adult patients. The researchers found that fresher RBCs offered no discernable benefit in this population. The study does demonstrate the importance of understanding the point at which the various changes that occur in stored RBCs increase the risk of adverse transfusion events. Other studies of stored blood have shown that markers of excessive hemolysis are not typically observed in recipients of RBCs stored for fewer than 35 days.

The Informing Fresh vs Old Red Cell Management (INFORM) trial aimed to study the effects of length of storage on post-transfusion mortality in a general population of adult patients requiring at least one RBC transfusion. Patients were randomized into two groups, those that would receive the freshest RBCs available (mean not given) and those who would receive the oldest RBCs available (mean 23.6 days old). No difference in mortality rates between the two groups was observed. However, like the ABLE trial, the question of whether the oldest RBCs, those stored to within a week of expiration, pose a risk to recipients was not addressed.

The focus of the Red Cell Storage Duration Study (RECESS) trial was the effect of RBC storage duration (ten days or fewer vs. 21 days or longer) in patients undergoing cardiac surgery, as measured by the Multiple Organ Dysfunction Score (MODS). No significant difference in outcomes was observed in the two patient groups. This study also suggests there is no increased risk associated with transfusion of older RBCs to cardiac bypass patients as the contribution to hemolysis from older red cell units is much smaller than the amount caused by the cardiac bypass pump (median pump time 140 min.).

The Tissue Oxygenation by Transfusion in severe anemia with Lactic Acidosis (TOTAL) trial was a non-inferiority study that looked at the effects of older (25-35 days) vs. fresher (1-10 days) RBCs on lactate levels in severely anemic children. This study was done on children in Uganda, most of whom had malaria or sickle cell disease. In Uganda, RBCs may only be transfused up to 35 days after collection. In patients with lactic acidosis secondary to severe anemia, the transfusion of both fresher and older RBCs reduced blood lactate levels equivalently.

Evidence presented in these recent studies suggests that transfusion of “very fresh” RBCs offers no benefit as compared with RBCs stored for up to 35 days. In these studies, very fresh referred to RBCs ≤ 10 days old. Questions still remain regarding the oldest of stored RBCs (those stored between 35-42 days). For some patient populations, RBCs stored longer than 35 days may or may not result in the same outcomes as fresher blood, and any benefits of a fresher blood strategy for very specific patient populations remain to be validated by randomized, controlled trials.

A steep decline in demand for blood components has occurred in recent years, but will this trend continue as the age of the world’s population shifts upward? This question is of pressing concern for blood centers, because data from the United States and 7 other countries shows that the need for blood increases for patients over the age of 50, with more than half of all red blood cell transfusions occurring in patients over the age of 60.

In an attempt to answer this question, the Biomedical Excellence for Safer Transfusion (BEST) Collaborative, an international research organization that studies ways to improve the safety of transfusion and transfusion-related services, recently studied ten years (2001-2011) of donor demographic data from 17 blood centers from 12 countries.

The overall population, and the blood donor population in particular, is aging in most of the countries represented in this study. For example, in the United Kingdom the median age of blood donors increased from 40 in 2001 to 44 in 2011 while the general population median age increased from 45 to 46. Over the same span of time, the percentage of the general population that is over the age of 60 increased by 1.5%. While in the United States the median age of blood donors actually decreased from 40 to 39 over this time frame, the median age of the general population increased from 43 to 45 and the percentage of those over 60 increased by more than 2%.

This trend will be problematic for blood centers since a significant percentage of dedicated older donors are expected to drop out of the donor pool as they continue to age. Blood centers will need to focus on the recruitment of more first-time blood donors, likely to be younger adults. The United States already relies heavily on this younger population, with about 20% of blood products coming from donors aged 16 to 24.

As the world’s population continues to increase in age, the need for blood products is expected to rise. Consequently, blood centers must continue to stress the recruitment and retention of blood donors of all ages.

Although extremely rare, variant Creutzfeldt Jakob Disease (vCJD) is one of the most notorious of a group of diseases called transmissible spongiform encephalopathies (TSEs). These conditions are also called “prion diseases”—prion being an abbreviation for “proteineous infectious particle”—because the causative agent is a pathogenic variant of a common protein normally found in the body. The pathogenic variant protein takes on a distorted configuration, causing nearby normal proteins to also become malformed. These prions can impact the brain and some tissues with high concentrations of lymphocytes such as the tonsils. Areas of the brain that are filled with these pathogenic proteins can collapse and form holes that give the brain of an affected person a sponge-like appearance. Sadly, these individuals deteriorate rapidly from dementia and severe coordination and motor skill impairment, and usually die within months or a few years following the appearance of symptoms. There currently is no known treatment available.

Variant CJD is the name of the human disease caused by eating meat from cattle with Bovine Spongiform Encephalopathy (BSE), also called “mad cow disease.” An epidemic of BSE occurred in the United Kingdom (UK) in the 1990s and was suspected to be caused by feeding healthy cattle meat and other tissue (called “offal”) from BSE-infected cattle. Consumption of BSE-contaminated beef was linked to vCJD in 1996. The number of vCJD cases in the UK peaked in 2000, with 28 reported deaths. vCJD can also be transmitted via transfusion, with the first cases reported in 2003 and 2004.

Although most reported cases of vCJD have occurred in the UK, there have been cases reported in other countries, typically in individuals who either lived in the UK for a period of time or who consumed beef from the UK. One person was born in the UK and moved to Florida in 1992. Another patient was born in the UK but lived briefly in Texas. A third case involved a patient who occasionally visited the US from Saudi Arabia where exposure most likely was from consumption of BSE-contaminated beef, and the latest case involves a US citizen who was born outside the US and was likely exposed before moving there.

Although several companies are working on diagnostic tests, there is currently no FDA-approved method to screen for TSEs. Filtration methods are also being studied to remove the prions from donated blood and blood components.

Because the incubation period of vCJD is not well understood but is estimated to average 11-12 years, it is difficult to ascertain how many people may have become infected with vCJD from eating BSE-contaminated beef. Although transfusion-associated vCJD, is rare, precautionary measures have been in place for many years. These measures include deferral of people who have lived in the UK during the period of greatest exposure risk (1980-1996) and other countries considered to have possible BSE risk, as well as those who received a blood transfusion in the UK since 1980. The FDA has recently drafted guidance that, if implemented, will change some of the vCJD deferral criteria.

Possible platelet inhibitor reversal effects of autologous platelet transfusions

Clopidogrel (Plavix) or ticagrelor (BRLINTA ®) have proven to be effective in decreasing the risk of thrombotic events such as heart attacks and strokes. These drugs compete with circulating adenosine diphosphate (ADP) to bind to the platelet P2Y12 receptor. As ADP serves as a platelet activator and promote platelet aggregation, blockage of blood vessels is reduced. A side-effect that complicates clinical management is bleeding. This is particularly true for a patient in need of surgical/medical intervention, increasing the risk of significant hemorrhage.

Current guidelines by the American College of Cardiology/ American Heart Association Task Force has suggested withholding such anti-platelet agents for several days (Clopidogrel or Ticagrelor – 5 days; Prasugrel – 7 days) prior to elective surgery. However, if surgery is needed emergently, AABB suggests platelet transfusions to reduce this bleeding risk.

The reviewed article demonstrates findings for one of the few published in vivo studies that evaluates outcome of transfused platelets, in individuals receiving anti-platelet agents. Healthy volunteer donors were administered Clopidogrel or Ticagrelor, 24 to 48 hours prior to receiving a previously collected autologous platelet transfusion. Blood samples were then assessed for platelet activity via light transmission aggregometry and platelet function assays. Results indicated slight normalization of platelet function for those receiving Clopidogrel, but none for Ticagrelor users. This was attributed to several factors, including Ticagrelor’s reversible binding and then redistribution to the transfused donor platelets, as well as the drug’s longer plasma half-life of 6 -12 hours (in contrast Clopidogrel’s 30 min -1 hour). Although further studies are needed, especially for those persons receiving anti-platelet drugs with similar pharmacological profile to Clopidogrel, future innovations such as antigen-binding-fragment (FAB) have the promise to serve as ‘antidotes’ for anti-platelet drug use.


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In addition to being a leader in the development and use of its own hemovigilance program, and engaging with its hospital partners in clinical research, the organization has a committed research team. The Red Cross has maintained an active central research and development program since 1968. Currently, the program is focused upon blood safety and product quality, with particular emphasis on managing infectious diseases and product storage. A total of more than 60 staff are engaged in our research facilities in the Washington DC area. Additional research is supported through our blood regions including two locations with the capabilities to evaluate red cell and platelet survival and recovery in vivo and one region involved in the NHLBI-funded REDS III program. Other efforts include world-class studies on immunohematology and on donor health, safety and motivation. The major portion of the central effort is funded by the Red Cross and there is additional support from government and industrial sources. Although the objectives of the research and development program are directed towards product safety and quality, much of the work is also published in academic journals. Through its commitment to investigation and innovation, Red Cross will remain at the forefront of efforts to improve collections, storage and distribution of blood and blood products and keep the US blood supply among the safest in the world.

Publications Corner

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