MISSISSIPPI VALLEY REGIONAL BLOOD CENTER
How life flows through our community.®
Blood Bulletin
America's Blood Centers® It's About Life.

Patient Blood Management (PBM) in the Setting of Adult Cardiovascular Surgery (CVS)

By Chris Gresens, MD, Senior Chief Medical Officer, North & West Divisions at Vitalant, Scottsdale, Arizona. The author discloses no conflicts of interest.

Perioperative Transfusion Management of CVS Patients

RBCs – Restrictive-vs-liberal transfusion triggers and impact of the "storage lesion": Randomized clinical trials (RCTs) have demonstrated equivalent clinical outcomes between: (1) adult CVS patients transfused restrictively vs. liberally (8 RCTs), and (2) CVS patients transfused with fresher vs. older RBCs (one RCT).[Shehata et al., Mazer et al. (2018), Steiner et al.] See table below for key findings from the TRICS (Transfusion Requirements in Cardiac Surgery) III and RECESS (Red Cell Storage Duration Study) trials.

TRICS III [Mazer et al, 2017;Mazer et al., 2018]

- Multicenter, noninferiority RCT involving 4,243 adult CVS patients
- Randomized to receive RBCs as follows:
  - For restrictive group (RG) – Transfuse for Hemoglobin (Hgb) <7.5 g/dL any time after start of anesthesia, or
  - For liberal group (LG) – Transfuse for Hgb of either:
    - <9.5 g/dL in the operating room or intensive care unit (ICU), or
    - <8.5 g/dL in the non-ICU ward.
- Primary composite outcome (28-day all-cause mortality or severe morbidity) was observed in 11.4% of the RG and 12.5% of the LG (p <0.001 for noninferiority).
- RBC transfusion rate was 52.3% in the RG vs. 72.6% for the LG (OR = 0.41; 95% CI: 0.37-to-0.47).[Mazer et al.; 2017]

Subsequent extension on these findings demonstrated that the composite outcome persisted at 6 months – 17.4% in the RG and 17.1% in the LG (OR of 1.02 and 95% CI of 0.87 to 1.18).[Mazer et al.; 2018]

RECESS .[Steiner et al.]

- Multicenter RCT involving 1,098 12-year-old-to-adult CVS patients
- No difference in primary endpoints between patients randomized to receive either:
  - "Shorter term" RBCs (≤10 days old), or
  - "Longer term" RBCs (≥ 21-days-old) RBCs.
- 7-day/28-day mortality rates were:
  - 2.8/4.4% for patients receiving fresher units, and
  -

2.0/5.3% for those receiving older units (p = 0.43/0.57)

Key Points

- Clinical outcomes in numerous randomized clinical trials for adult CVS patients receiving red blood cells (RBCs) are comparable between:
  - Those transfused restrictively versus liberally; and
  - Those transfused with fresher versus older RBCs.
- Indications for platelet and plasma transfusions in this population are comparable to those applied to other bleeding/surgical patients – i.e.,
  - Transfuse platelets for count <50,000/µL and/or bleeding when patient's platelets are dysfunctional (e.g., from anti-platelet agents); and
  - Transfuse plasma for significant coagulopathies (e.g., INR > 2.0).
- Perioperative PBM in this population focuses on minimizing the extent/impact of preoperative anemia and modifiable bleeding risks.

Platelet and Plasma Components:

The evidence base for use of platelet transfusions for adult CVS patients is lower quality than for RBCs. Indications mirror those for other bleeding/surgical patients – e.g., transfuse for platelet count <50,000/µL and/or microvascular bleeding when a patient's platelets are found to be substantially dysfunctional (confirmed by laboratory testing). Plasma transfusions are recommended for bleeding, coagulopathic patients (e.g. INR >2.0).[Bandarenko] A strong consensus exists for the balanced ratio-driven use of platelets and plasma with RBCs during the management of massive transfusions.[Delaney et al., Boer et al., Ferraris et al.]

PBM IN CVS

The central thrust of CVS-related PBM is to prevent and control massive bleeding. These efforts should begin weeks preceding surgery and continue throughout the postoperative period.

Preoperative PBM – Key Areas of Importance

Coagulation testing: This may involve: (1) "traditional" testing, (2) whole blood viscoelastic (VE) tests, and/or (3) platelet function (PF) assays. Traditional testing (e.g., INR, aPTT, and platelet count) is performed primarily for goal-directed purposes (e.g., assessing the INR of patients on warfarin to determine if any correction is required). While routine *pre*operative VE and PF testing do not appear helpful, VE testing is believed by many to play an important *intra*operative role; *pre*operative PF testing, moreover, has appeared effective

in predicting bleeding risk in patients on P2Y12 inhibitors (e.g., clopidogrel). [Boer et al.]

Preoperative management of coagulation issues: This is directed primarily toward "on-board" antithrombotic agents. Determining when and how to modify or suspend use of these drugs depends on many factors including the type of surgery, the underlying condition, and the medication(s) being used. For example, aspirin used by pre-coronary artery bypass graft (CABG) patients generally should not be discontinued; however, it usually *should* be stopped 5 days preoperatively for patients at high risk for bleeding (or those who refuse blood) prior to non-coronary procedures.[Boer et al., Ferraris et al.]

Addressing preoperative anemia: Such anemia is associated with increased RBC transfusion needs, acute kidney injury, and death. Management should focus on the cause – e.g., iron supplementation for iron deficient anemia. Moreover, erythropoiesis stimulating agents have proven effective in reducing perioperative transfusion requirements in some CVS patients with anemia unrelated to iron deficiency. Preoperative RBC transfusions are reserved for patients with symptomatic or life-threatening anemia who require emergent CVS.[Boer et al., Ferraris et al.]

Intra/postoperative PBM – Key Areas of Importance

Topical hemostatic agents: These play varying roles in preventing and controlling intraoperative bleeding and include: topical fibrin (and similar biological) sealants, topical antifibrinolytic drugs, passive hemostatic agents (that "do not contain biologically active clotting factors" – e.g., collagen and gelatines), and synthetic and semi-synthetic sealants. [Boer et al.]

Intraoperative VE testing: A recent meta-analysis of 15 RCTs involving 8,737 patients suggested that such testing leads to reduced RBC and platelet transfusion requirements but "did not improve other important clinical outcomes."[Serraino]

Intraoperative anticoagulation: This is still accomplished near-exclusively using unfractionated heparin. The activated clotting test (ACT) has been the primary means to monitor heparinization and determine when to administer protamine; however, the evidence-based consensus is gravitating toward use of direct measurements of heparin concentration and/or anti-factor Xa activity. For patients with antithrombin (AT) deficiency, replacement with AT factor has become standard of care. The use of the direct thrombin inhibitor bivalirudin should be considered for patients with any history of heparin-induced thrombocytopenia who need on-pump surgery.[Boer et al.]

Autologous transfusions: Pre-surgical autologous donation, intra or post-operative cell salvage, and acute normovolemic hemodilution are options for patients who do not wish to or cannot (e.g., patients with complex compatibility problems) receive allogeneic blood and/or whose surgery is expected to have a moderate to heavy bleeding potential.[Boer et al.]

Protocol-driven approaches for determining when to transfuse and/or administer selected procoagulant drugs: Significant reductions in allogeneic transfusion, improved clinical outcomes and reduced cost were reported when VE and PF point-of-care testing was performed in concert with pragmatic clinical decision making.[Pearse et al.] Moreover, as blood conservation strategies continue to improve, Jehovah's Witness patients and others for whom transfusion is not an option can in many instances anticipate CVS outcomes similar to those of their transfusion-accepting matched counterparts.[Guinn et al.] Lastly, the use of leukoreduced cellular blood components, which has long been known to mitigate the risks for HLA alloimmunization and febrile nonhemolytic transfusion reactions, also is recommended by many experts due to its potential for reducing the risk for postoperative infections. [van de Watering et al.]

Drug-Facilitated Coagulation Management – Key Areas of Importance

Antifibrinolytic agents play an active role in hemorrhage reduction for many CVS patients. *Factor XIII concentrates* may be useful for bleeding of post-cardiopulmonary bypass in patients who have factor XIII concentrations <70%. *Fibrinogen replacement* (using fibrinogen concentrates in the EU versus cryoprecipitate in America) is recommended for bleeding patients with fibrinogen levels <150 mg/dL. Four-factor *prothrombin complex concentrates* are used in emergency situations to reverse vitamin K antagonists when timing precludes the sole use of IV vitamin K (and also to counteract the effect of some novel oral anticoagulants). Bleeding patients with some inherited or acquired platelet function defects (e.g., some cases of type 1 or 2 von Willebrand disease, mild-to-moderate hemophilia A, and aspirin use) may benefit from the use of *desmopressin* (DDAVP). Patients with treatment-resistant, severe microvascular bleeding who have failed all other procoagulant treatments may benefit from *recombinant factor VIIa*.[Boer et al.]

References:

1. Bandarenko N, King KE (editors). Blood Transfusion Therapy – A Physician's Handbook, 12th ed. AABB, Bethesda, MD, 2017.
2. Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothor Vasc Anesth 2018;32:88-120.
3. Ferraris VA, Brown JR, Despotis GJ, et al. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. Ann Thorac Surg 2011;91:944–82.
4. Guinn NR, Roberson RS, Whote W, et al. Costs and outcomes after cardiac surgery in patients refusing transfusion compared with those who do not: a case-matched study. Transfusion 2015;55:2791-8.
5. Mazer Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. NEJM 2017;377:2133-44.
6. Mazer CD, Whitlock RP, Fergusson DA, et al. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. NEJM 2018;379:1224-33.
7. Pearse BL, Smith I, Faulke D, et al. Protocol guided bleeding management improves cardiac surgery patient outcomes. Vox Sang 2015;109:267-79.
8. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Brit J Anaesth 2017;118:823–33.
9. Shehata N, Mistry N, da Costa BR, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. Eur Heart J (electronically published August 10, 2018 – https://doi.org/10.1093/eurheartj/ehy435).
10. Steiner ME, Ness PM, Assmann SF, et al. Effects of red cell storage duration on patients undergoing cardiac surgery. NEJM 2015;372:1419-29.
11. Van de Watering LMG, Hermans J, Houbier JGA, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 1998;97:562-8.

Blood Bulletin is issued periodically by America's Blood Centers. Publication Committee Chair: Chris Gresens, MD; Editor: Mack Benton. The opinions expressed herein are opinions only and should not be construed as recommendations or standards of ABC, ABC SMT Committee, or its board of trustees. Publication Office: 725 15th St., NW, Suite 700, Washington, DC 20005. Tel: (202) 393-5725; Fax: (202) 393-1282; E-mail: memberservices@americasblood.org.