Getting it Right: Optimizing Transfusion Management during the Procedure

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Abstract: There is little doubt that blood transfusions have saved many lives in cases of acute hypovolemia and anemia, but both the literature and practitioners still do not agree as to what the appropriate indicators for transfusion are in a cardiac surgical patient. Furthermore, there are those who claim that the benefit of blood transfusions has never been conclusively demonstrated, and evidence of transfusion related harm continues to accumulate. Cardiac surgical patients may be transfused not only because of bleeding but also due to hemodilution from preoperative and intraoperative intravenous fluids and pump primes in conjunction with a possible preoperative anemia. Getting transfusion right to improve our practice has to be approached multifactorially. The use of prophylactic dosing of blood products has been suggested to be ineffective in reducing blood loss. There are many factors that impact transfusion rates including determining the optimal hematocrit where it is highly unlikely that one figure will be applicable to all patients. The formulation of transfusion guidelines and algorithms that have been agreed upon by all practitioners involved in the care of cardiac surgical patients may have a positive effect—if everyone agrees to transfuse patients via the formulated guidelines or algorithms. Importantly, no one individual should be able make the decision on whether a patient requires a blood transfusion—it must at all times be a team decision, whether in the operating room or intensive care unit.

Keywords: cardiopulmonary bypass, hematocrit, transfusion.

There is little doubt that blood transfusions have saved many lives in cases of acute hypovolemia and anemia, but both the literature and practitioners still do not agree as to what the appropriate indicators for transfusion are in a cardiac surgical patient. Furthermore, there are those who claim that the benefit of blood transfusions has never been conclusively demonstrated, and evidence of transfusion related harm continues to accumulate (1).

Repeat cardiac surgery is associated with increased bleeding and significant increases in patient morbidity and mortality (2–4). Furthermore, a minority of patients having cardiac procedures (15–20%) consume more that 80% of the blood products transfused (5).

Cardiac surgical patients may be transfused not only because of bleeding but also due to hemodilution from preoperative and intraoperative intravenous fluids and pump primes in conjunction with a possible preoperative anemia. Getting transfusion right to improve our practice has to be approached multifactorially (6). Techniques that have been shown to be useful are preoperative assessment (and treatment when required), intra-operative techniques for transfusion reduction, and an overall transfusion protocol.

We must first address pre-cardiopulmonary bypass (CPB) hemodilution by reducing preoperative fluids. As pump primes are arguably the largest source of hemodilution, perfusionists should endeavor to reduce pump primes by reducing circuit size and using methods such as autologous retrograde priming.

OPTIMAL HEMATOCRIT FOR CARDIOPULMONARY BYPASS

Complications associated with hemodilution include postoperative renal failure, increased stroke rate, myocardial infarction, low cardiac output, prolonged ventilation, pulmonary oedema, vital organ dysfunction, and neurocognitive dysfunction. All of these complications have been associated with hematocrit (Hct) levels less than 22% (7–11).

Von Heymann et al. evaluated oxygen delivery and consumption and clinical outcomes in 54 low risk patients during CPB in a prospective randomized trial. Patients were divided into two groups: moderate Hct (25% Hct, n = 28)
Pre-operative preparation and assessment is essential to optimize a patient for surgery. The use of erythropoietin in cardiac surgery has yet to show any benefit mainly due to the lack of any large randomized study. The majority of small studies are anecdotal and deal mainly with anemia in the Jehovah Witness population—a very small group requiring cardiac surgery. However, Alghamdi et al. performed a meta-analysis of 11 randomized controlled trials, reporting comparisons between erythropoietin and control groups (12). In total, 471 patients were given erythropoietin, and 237 patients formed the control group. They concluded that the administration of erythropoietin before cardiac surgery was associated with a significant reduction in the risk of exposure to allogeneic blood transfusion (12). The use of erythropoietin in cardiac surgery may have a place in dealing with anemia in the non-acute patient as its use is required several days prior to surgery to have the desired effect.

**USE OF INTRAVENOUS IRON IN ANEMIA**

A multidisciplinary panel of physicians was convened by the Network for Advancement of Transfusion Alternatives in 2008 to review the evidence on the efficacy and safety of intravenous iron to increase hemoglobin levels and reduce blood transfusion in patients undergoing surgery. Reporting their findings, Beris et al. evaluated two randomized controlled trials and six observational studies in orthopedic and cardiac surgery, finding that there was little evidence to support the use of intravenous iron (13).

**FRESH FROZEN PLASMA**

Casbard et al. systematically reviewed the role of prophylactic fresh frozen plasma (FFP) in decreasing blood loss and correcting coagulopathy in cardiac surgery (14). They performed a comprehensive literature search of all available randomized controlled trials of the use of FFP in cardiac surgery from January 1966 to August 2003. Six small trials were found that included a total of 363 patients with six different dose regimens of FFP. The authors’ concluded that there was no evidence that prophylactic use of FFP affected peri-operative blood loss in cardiac surgery (14).

Stanworth reviewed the evidence-base of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy (15). He suggested that the evidence indicated that FFP is commonly used during cardiac surgery and a number of published randomised clinical trials have assessed the benefit. However, random clinical trials evaluating prophylactic use of FFP with either no FFP or a non-plasma produce after CPB have not shown evidence of a significant effect on blood loss or transfusion requirement (15).

Abdel-Wahad and colleagues prospectively audited FFP transfusions at their hospital for 13 months to determine the effect of FFP on coagulation variables and correlation.
with bleeding in patients with mildly prolonged coagulation values. Of the 1091 FFP units transfused, follow-up coagulation values within 8 hours were available for 121 patients (324 units). Transfusion of FFP resulted in normalization of international normalized ratio (INR) values in only 8% of patients (confidence interval (CI) 20–4.5) and decreased the INR values halfway to normal in 15% of patients (CI 9.7–22.5). The median decrease in INR was 0.07. Pre-transfusion PT-INR, partial thromboplastin time, platelet count, and creatinine values had no correlation with red blood cell loss. They recommend that FFP infusion should be restricted to bleeding patients with significant coagulation defects (i.e., INR >2) (16).

Bolliger and colleagues performed an in-vitro study hypothesizing that there is a minimal fibrinogen concentration in diluted whole blood above which the rate of clot formation approaches normal (17). The authors concluded that the target plasma concentration for fibrinogen replacement was greater than 200 mg/dL, as only these concentrations optimized the rate of clot formation. This concentration is twice the level suggested by current Australian transfusion guidelines <1.0 g/L. Although improved, clots were prone to fibrinolysis indicating that the efficacy of fibrinogen therapy may be influenced by existing fibrinolytic tendency occurring during dilutional coagulopathy (17).

An issue when using FFP is that it requires thawing, which delays availability and encourages the practice of unnecessary ordering on the presumption that it may minimize delays if it really is required. Once thawed, it is considered that it must be used or discarded resulting in FFP being transfused rather than wasted. Von Heymann et al. assessed the activity of clotting factors in FFP once thawed and then stored at 4°C over 6 days (18). Plasma of 20 healthy donors was analyzed. Immediately after thawing there was a significant decrease in fibrinogen and most other clotting factors. However, over the following 6 days, fibrinogen, ATIII, and vWF levels remained stable. All clotting factors and inhibitors remained within reference range as determined by quality assurance regulations and no FFP bag showed bacterial contamination (18).

**CRYOPRECIPITATE**

Fresh Frozen Plasma contains fibrinogen at near-normal plasma levels so it will correct low fibrinogen levels if the volumes for infusion are adequate. Cryoprecipitate should not be considered solely as a more concentrated form of FFP as it only contains significant levels of FVIII, vWF, fibronectin, FXIII, and fibrinogen. Therefore, cryoprecipitate is not a source of all coagulation factors and is not an appropriate replacement therapy for patients with global coagulation deficiencies (15).

**FACTOR CONCENTRATES**

Haemocomplettan® P (CSL Behring, Marburg, Germany) is a concentrated formulation of pooled plasma-derived human fibrinogen subjected to pasteurization and purification for virus inactivation and removal. This fibrinogen concentrate has been associated with reduced transfusion requirements and 24-hour postoperative bleeding in patients undergoing cardiac surgery (19).

**PROTHROMBIN COMPLEX CONCENTRATES**

Fraser, Corke, and colleagues performed a retrospective audit of the administration of Prothrombinex-HT in 60 patients following adult cardiac surgery (20). No major prothrombotic complications were noted. Two patients had superficial thrombophlebitis. Blood product consumption and haematological parameters were markedly reduced after administering Prothrombinex-HT.They concluded that the use of Prothrombinex-HT was not associated with significant prothrombotic complications. However, the current limited evidence of its efficacy suggests that it should be further evaluated in the setting of cardiothoracic surgery (20).

Leissinger et al. recently reviewed the literature on the role of Prothrombin Complex Concentrates (PCC) in reversing warfarin anticoagulation—particularly as they consider over-anticoagulation with warfarin a common problem (21). The goal of urgent warfarin reversal is to elevate or replace vitamin K-dependent clotting factors. They concluded that PCC offer a rapid and specific method for replacing vitamin K-dependent clotting factors and restoring normal hemostasis in the context of over-anticoagulation. In those studies in which PCC were compared with FFP, PCC were found more effective in shortening the time to INR correction and were associated with low risk of thrombotic adverse events. However, evidence-based treatment guidelines are needed to optimize the use of PCC for warfarin reversal (21).

**RECOMBINANT FACTOR VIIa**

Diprose and Herbertson et al. concluded that activated recombinant factor VII (rFVIIa) given after CPB reduces allogeneic transfusion in complex non-coronary cardiac surgery in their randomized double-blind placebo-controlled pilot study. Reported rFVIIa levels may be effective in reducing this need for transfusion (22).

An observational study by Karkouti et al. sought to identify the off-label use pattern of rFVIIa in cardiac surgery and to identify predictors of its effectiveness and risk (23). They concluded that rFVIIa is used primarily when standard interventions have failed to control bleeding. In this setting, rFVIIa is associated with reduced blood product transfusions and, after risk adjustment, does not appear to be associated...
with increased or decreased complication rates. The effectiveness of the drug may be enhanced if it is given early in the course of refractory blood loss in the setting of adequate amounts of circulating coagulation factors (23).

PLATELETS

Platelet transfusions have been reported to be associated with increase mortality and morbidity (24). Conversely, others have claimed that platelet transfusions do not increase morbidity (25). Australian blood transfusion guidelines recommend that a platelet transfusion is required when counts fall below 50–100 × 10^9/L for surgical procedures that have a high risk of bleeding. Evidence-based platelet transfusion guidelines by Sherrill (2007) suggest that a 10 × 10^9/L prophylactic platelet transfusion trigger has been documented to be both hemostatically efficacious and cost effective in reducing platelet transfusion requirements (26).

Poor responses to platelet transfusions are often multifactorial and include human leukocyte antigens, splenomegaly, ABO mismatching, use of heparin or amphotericin, bleeding, fever, graft vs. host disease, and vasculitis disease (26). Blajchman et al. claim that the need for platelet transfusions in the face of severe bleeding is undisputed; however, important questions remain about what constitutes clinically significant bleeding and whether a strategy of prophylactic platelet transfusions is effective in reducing the risk of bleeding in clinically stable patients (27).

The other consideration is the resumption of function of transfused platelets. Opinions vary that function returns in a period of 2–6 hours but these views have not been addressed in the literature. We have noticed that in some patients whilst on CPB, there is a functioning coagulation system when assessed by heparinase thromboelastograph. Upon prophylactically administering platelets post CPB, the patient appears to develop a coagulopathy for no apparent reason. We suspect this is caused by a dilutional effect of the transfused products.

DESMOPRESSIN

Some studies suggest a reduction in bleeding occurs with the use of desmopressin during cardiac surgery (28). Further clinical trials include the current study at St. Olav’s Hospital Trondheim, Norway investigating if desmopressin has any clinical benefit in reducing transfusion and blood loss in cardiac surgical patients.

TRANEXAMIC ACID

The effect of tranexamic acid on the use of blood products and post-operative bleeding after primary cardiac surgery in 4191 patients was studied by Vuylsteke et al. The probability of receiving a transfusion or returning to theatre for bleeding was significantly lower in patients receiving tranexamic acid. The administration of tranexamic acid also significantly decreased blood loss. They concluded that tranexamic acid decreased the number of patients exposed to a transfusion and the return to theatre for bleeding at their institute (29).

The use of tranexamic acid to reduce postoperative drainage and allogenic blood transfusion requirements in patients undergoing on-pump primary coronary bypass surgery was also investigated by Maddali and Rajakumar. Postoperative drainage was significantly less and blood conservation considerably better in the tranexamic acid group. They concluded that post-bypass hemostasis was achieved faster, fibrinolysis was less, and there was no evidence of an increased incidence of graft occlusion in the group given tranexamic acid (30).

PREDICTING BLEEDING

Those patients that are likely to be transfused should be identified. However, waiting for the patient to arrive in the operating room does not give enough time to properly assess and reduce their risk of requiring a transfusion. How can we predict that a patient will require blood products?

Preoperatively assessing the patient may yield a patient history that suggests a propensity for bleeding. The patient can be asked if they bruise easily, suffer from mucosal bleeding or spontaneous soft tissue bleeding or delayed healing and do they take any herbal medicines? Should protocols be established that will trigger a hematology consult during admission? Cardiopulmonary bypass is an associated cause that predisposes the patients to significant bleeding both intra-operatively and post-operatively. Ways to clinically predict transfusion risk include systems such as the Transfusion Risk Understanding Scoring Tool (TRUST), which has been shown to be effective (31).

Ranucci et al. suggested that current prediction scores are far too complex and that the easier scores are required. They suggest the following predictors for transfusion risk: age >67 years, weight <60 kg for females and <85 kg for males, preoperative Hct, female-gender, and complex surgery. When compared with the other three existing scores, this Transfusion Risk and Clinical Knowledge score had comparable or better predictive power and calibration (32).

Perhaps the best method of transfusion prediction may lie at the time of surgery with the use of point care analysers (33). Coagulation management in the operating room answers problems that are often 2-fold. First, the waiting time for laboratory results delays treatment and often leads to the over or under use of blood products, secondly helps assess the rapidly changing state of the coagulation components immediately post CPB or in the bleeding surgical
patient. The advantage of point of care coagulation analyzers is that the tests can be baselined immediately before CPB and repeated during the rewarming phase of bypass to identify potential problems. Whilst heparinized, platelet counts and measures of clot integrity can be still performed with the use of heparinase cups in the thromboelastograph. At this time, in conjunction with transfusion algorithms, it may be possible to predict whether blood products or factor supplements will be required (34,35).

In a study by Avidan and colleagues, a management algorithm based on point of care testing was tested to see if it would reduce blood loss and blood component use after routine coronary artery bypass grafts when compared with an algorithm based on routine laboratory results, or with clinical judgment (36). The results in all three groups showed a similar median blood loss. The transfusion of packed red blood cells and components were significantly higher in the clinician discretion group but showed no difference between the two algorithm groups. The authors concluded that algorithms based on either point of care or laboratory guidelines do not decrease blood loss, but do reduce the transfusion rate of red cells and blood products as compared with clinical discretion (36).

SUMMARY

There is no one clear answer in how to optimize transfusion management during the procedure. However, it is becoming clear that the evidence is growing and that there is a need to limit or avoid transfusions (37–39). Even exposure to one or two units of red blood cells may be associated with a 16% increased hazard of decreased survival after cardiac surgery (40). Additionally, the age of the blood product being transfused is another confounder in postoperative morbidity (41–43), in addition to the ongoing unknown risk associated with blood borne pathogens.

The transfusion literature often refers to the empiric transfusion practices in the operating rooms where transfusions are too often based on observation and routine practices rather than measurement (44,45). The use of prophylactic dosing of blood products has been suggested to be ineffective in reducing blood loss (15). There are many factors that impact transfusion rates including determining the optimal Hct where it is highly unlikely that one figure will be applicable to all patients. The formulation of transfusion guidelines and algorithms that have been agreed upon by all practitioners involved in the care of cardiac surgical patients may have a positive effect—if everyone agrees to transfuse patients via the formulated guidelines or algorithms. Importantly, no one individual should be able make the decision on whether a patient requires a blood transfusion—it must at all times be a team decision whether in the operating room or intensive care unit.

It is often stated that a technique or drug to avoid transfusion has shown only a small benefit and is cost prohibitive, but it may be the accumulation of small benefits that will significantly reduce or eliminate transfusions. We must reconcile the cost of reducing transfusions with the cost of the morbidity and mortality associated with giving blood products.

REFERENCES