Fresh Frozen Plasma-Based Versus Factor-Based Treatment Of Perioperative Coagulation Disorders

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Learning Objectives:

- Existing and possible future factor-based therapies and their advantages (benefits) and disadvantages (risks) compared with blood product administration in the bleeding surgical patient.
- Laboratory tests and the test values that can help in determining when factor-based therapies should be administered.

Background:

In the past few years, the de facto definition of hemostasis has been transformed from “cessation of bleeding” to be defined as the “balance between bleeding to death and clotting to death”. With that in mind, coagulation disorders can be in the form of hypocoagulation (bleeding diathesis), hypercoagulation (thrombosis) or a mix of two, and they can be hereditary or acquired. The focus here is on the acquired hypocoagulation disorders or coagulopathies in patients undergoing cardiovascular and high risk of bleeding surgeries. These disorders are particularly important, since they can increase the risk of surgical blood loss and the risk of exposure to allogeneic blood products, and contribute to increased morbidity and mortality in these patients. Additionally, specific techniques used in the patients undergoing cardiovascular surgeries (e.g. cardiopulmonary bypass [CPB]) and medications
commonly administered in these patients (e.g. warfarin) as well as some intravenous fluids used
during surgery can result in coagulopathies, and possibly increase the risk of bleeding.

**Common Laboratory Tests:**

Coagulation occurs as a result of a cascade of enzymatic reactions, activated by specific
triggers (e.g. exposure of tissues to blood), and propagated in a controlled manner to form a solid clot.
Several factors are involved and laboratory tests have been developed to assess them, as indicators of
overall coagulation status. Routine laboratory tests for coagulation assessment include Prothrombin
Time (PT) and activated Partial Thromboplastin Time (aPTT), commonly normalized into
International Normalized Ratio (INR). Despite their frequent use particularly in the perioperative
setting and to guide anticoagulant therapy, their correlation with the risk of bleeding is generally poor
and not fully established [1,2]. These tests primarily assess the intrinsic and extrinsic pathways of
coagulation (i.e., the pro-coagulant arm of hemostasis) and some of the factors involved (but not all,
namely vWD and FXIII) [3], and their values become abnormal in patients receiving oral
anticoagulants or heparin, patients with vitamin K deficiency or end-stage liver disease, and patients
with autoantibodies against the coagulation factors (both pro and anti coagulants). [4,5]. At the end of
the coagulation cascade, thrombin (FII) is generated which converts fibrinogen to fibrin to form the
blood clot. Hence, fibrinogen deficiency can hinder clot formation and measurement of fibrinogen
level is another laboratory test used in the perioperative setting. Apart from congenital deficiencies,
fibrinogen deficiency can occur in context of blood loss and hemodilution resulting in poor to no clot
formation. Finally, platelets play an essential role in coagulation and an adequate quantity (depending
on the context) of functioning platelets are required for effective clot formation. Platelet count is done
as part of routine complete blood count in patients undergoing surgery [4]. Functional tests that
address both arms of hemostasis such as thromboelastography and thromboelastometry are becoming
increasingly available in the intraoperative setting. Thromboelastography and thromboelastometry
have the advantage of rapidly assessing the coagulation status of whole blood at the bedside, and they
have been shown to provide much more relevant information than PT, PTT and platelet counts to guide the clinician in a “goal directed” management and thus reduce or eliminate transfusions in these surgeries [6].

**Management of Coagulopathies:**

Urgent management of coagulopathies in presence of active bleeding often involves replacement and replenishment of the missing (or reduced) coagulation factors. Although some uses are considered off-label, various agents are available and used in the urgent management of patients with coagulation disorders in the perioperative setting, namely, plasma (fresh frozen plasma [FFP] or other variants), cryoprecipitate, fibrinogen, factor XIII, prothrombin complex concentrate (PCC), and recombinant factor VIIa. Evidence-based guidelines for some of these agents are available to direct the use of proper agents in proper patients. In each case, the factors affected, the factors present in the agent to be used, other potential alternatives, and logistics of administration should be considered.

- **Fresh Frozen Plasma:**

  Plasma transfusions share many of the risks and complications associated with other allogeneic blood products, particularly transfusion-related acute lung injury (TRALI), febrile and allergic reactions, and transfusion-associated circulatory overload (TACO) and they face similar logistic challenges. Plasma products available from transfusion services include FFP (plasma frozen within 8 hours of collection), FP24 (plasma frozen within 24 hours), thawed plasma (TP; thawed FFP or FP24 with an extended shelf life), and liquid plasma (plasma units never frozen) [7,8]. Issuing plasma products involves a number of time-consuming steps which may cause issues in urgent cases, where plasma is more likely to be indicated. Patient’s blood group must be identified and cross-matched and several minutes are needed to thaw the frozen plasma. Even when the plasma is readily available, the administered dose of plasma is often inadequate to achieve the intended therapeutic objective. Additionally, each plasma unit is approximately 200-250 mL and giving the correct
therapeutic dose may increase the risk of volume overload particularly in elderly patients with co-
morbidities such as atrial fibrillation and cardiovascular disease [9]. Finally, available evidence
suggests an inconsistent ability to correct mild-to-moderate elevations in the PT/INR or PTT with the
administration of FFP, partly because an FFP unit frequently has an INR in the upper normal or even
above normal ranges, and the INR increased with the time elapsed since thawing the plasma units
[6,10-13].

Recent evidence-based guidelines have recommended plasma for patients requiring massive
transfusion and patients with warfarin therapy–related intracranial hemorrhage, but could not
recommend for or against transfusion of plasma to patients undergoing surgery in the absence of
massive transfusion, or to reverse warfarin anticoagulation in patients without intracranial
hemorrhage. The guidelines did not recommend plasma transfusion for other selected groups of
patients, although patients undergoing cardiovascular surgeries were not specifically mentioned [14].

Based on these and other guidelines, current clinical indications for plasma are mainly limited
to serious bleeding or surgical procedures in context of multiple or single coagulation factor
deficiencies (congenital, acquired, dilutional, or due to consumption such as in disseminated
intravascular coagulation) when safer fractionated products are not available [15-17]. In patients with
microvascular bleeding following CPB, plasma may limit coagulopathy [18]. Plasma generally should
not be considered for warfarin reversal unless PCC is not available and/or severe bleeding is present
[19-21].

Around one-fifth of patients undergoing CPB have an inadequate response to heparin (i.e.
heparin resistance) and plasma may be used to treat heparin resistance, but Antithrombin concentrate
(AT3) is preferred since there is reduced risk of transmitting infections and other blood complications
and AT3 does not result in volume overload [22]. Recently, recombinant form of AT3 has also
become available.

Plasma units are commonly included in massive transfusion protocols, mostly to avoid or
alleviate dilutional coagulopathy. Although some studies indicate better outcomes with higher
FFP:RBC ratios, conflicting reports exist on the benefits of FFP in this context [23-26]. Finally,
plasma is not indicated for correction of coagulopathy in the absence of bleeding, warfarin reversal
when vitamin K can be safely used, and as a prophylactic treatment to reduce blood loss and allogeneic transfusions in cardiovascular surgery patients without coagulopathy [15,27,28].

- **PCC:**

  PCC contains relatively high levels of factors II, IX and X, and in some preparations, factor VII. These products were historically used for FIX replacement, and thus the vial potency labeling is commonly based on units of FIX present. Compared with plasma, PCC is administered in much smaller volumes without consideration of blood groups and it acts faster. Although PCCs are derived from pooled human plasma, multiple steps of viral inactivation are applied in addition to the donor screening, and therefore, PCCs are relatively free of many safety issues of plasma as an allogeneic blood component. PCC poses some thrombotic risks, usually in patients with other prothrombotic risk factors, but Information regarding thrombotic risks in patients having cardiac operations is lacking [29]. It should be noted that current PCC preparations available in the United States contain reduced amounts of Factor VII (hence called, “three-factor” PCCs) compared with the PCC units available in Europe (so-called “four-factor PCCs), possibly reducing their effectiveness in warfarin reversal 30,31].

  Some recent guidelines indicate that PCCs are preferred to plasma for warfarin reversal in bleeding patients, based on several lines of evidence [32-34]. Three-factor PCCs are indicated in the prevention or treatment of congenital FX or prothrombin deficiency. In Europe and Canada, four-factor PCCs are used for acute reversal of vitamin K antagonists, but as mentioned earlier, 4-factor PCCs are not licensed for warfarin reversal in the US, and they are currently undergoing clinical trials for this indication in the US [35]. The off-label use of three-factor PCCs in acute warfarin reversal has been reported, but given the low FVII content, recovery of PT/INR may be limited without additional FFP [35]. Boulis et al. showed in a randomized, controlled study on patients receiving vitamin K antagonist that PCC achieved significantly shorter time to correct INR compared with FFP [36]. Schick et al. reviewed 50 surgical patients requiring urgent warfarin reversal who received a four-factor PCC infusion, and reported that PCC significantly reduced INR and prevented or stopped major surgical bleeding, with no associated thrombotic event [38]. In a prospective randomized trial,
Demeyere et al. compared a four-factor PCC with FFP in 44 patients requiring urgent reversal of warfarin anticoagulation in order to undergo open-heart surgery, and showed a faster and more effective outcome with administration of PCC versus FFP [38]. Studies have reported successful hemostatic management using PCCs in dilutional coagulopathy due to massive transfusion, post-CPB, and liver failure, although risk-benefit profile has not been established yet [39-41].

- **Cryoprecipitate:**

  Cryoprecipitate is rich in FVIII, vWF, FXIII, and fibrinogen, and it was originally used for the replacement of congenital deficiency of FVIII (hemophilia A), vWF (von Willebrand disease), FXIII, or fibrinogen, but more specific fractionated and recombinant factors are now available and preferred for these indications [42-44]. Cryoprecipitate does not contain sufficient levels of vitamin K-dependent factors and thus is not an option for warfarin reversal. Currently, cryoprecipitate is mainly used to manage bleeding due to acquired hypofibrinogenemia (<100–150 mg/dL) in patients undergoing an invasive procedure, as it acts faster than FFP. However, it may take more time to thaw multiple units of cryoprecipitate and more importantly, unavailability of virus-inactivated cryoprecipitate and multiple donor exposures are serious concerns [45], and availability of fibrinogen concentrates is likely to further limit the use of cryoprecipitate, although current product labeling focuses on patients with congenital fibrinogen deficiencies. The plasma levels of fibrinogen required to minimize perioperative bleeding is not well established and they range from 80–100 mg/dL to 200 mg/dL or more in recent studies, including in patients undergoing cardiac surgery [15,46-51].

- **Fibrinogen Concentrate:**

  Fibrinogen concentrate is currently indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. However, a number of recent studies indicate its safety and efficacy in acquired hypofibrinogenemia, such as in dilutional coagulopathy. It is made from pooled human plasma, and as such, could carry
some risk of transmitting infectious agents such as viruses and Creutzfeldt-Jakob disease (CJD) agent despite pasteurization.

A number of studies have supported the effectiveness of fibrinogen concentrate in management of acquired hypofibrinogenemia, and in many European countries, cryoprecipitate is increasingly being replaced by fibrinogen concentrate in treatment of patients with acquired hypofibrinogenemia, and it has been suggested as a possible alternative to FFP as well [52]. A number of recent studies have suggested that prophylactic fibrinogen concentrate may be effective in reducing blood loss and transfusion rates in patients undergoing cardiovascular surgeries, but more studies are needed [53,54].

- **Recombinant Activated Factor VII (rFVIIa):**

  Current FDA-approved indications of rFVIIa include treatment of bleeding and prevention of bleeding in surgical or invasive procedures in patients with hemophilia A or B who have antibodies to factors VIII, IX or with acquired hemophilia; and treatment of bleeding and prevention of bleeding in surgical or invasive procedures in patients with congenital FVII deficiency. Additionally, several case reports, reviews and meta-analyses have discussed the off-label use of rFVIIa to control bleeding in other patients, although the available evidence is still far from being definitive. Few RCTs conducted to date suggest some benefits in patients with refractory, life-threatening hemorrhage including those with traumatic injuries and after cardiac surgery. Some reports indicate efficacy in management of warfarin-associated bleeding, although current guidelines limit such use to only when PCC or plasma are not available. PT and INR are rapidly shortened after rFVIIa administration, although they do not necessarily correspond to hemostasis and bleeding [46]. In a pediatric congenital heart surgery population, rFVIIa administration at a small dose after protamine did not affect blood loss, transfusion or outcome [55]. In another small study in adult cardiac surgery patients, there were no differences in outcome in the rFVIIa arm [56]. Subsequently, prophylactic or routine use of rFVIIa in cardiac surgery was not recommended by a consensus group [57], although a recent study of bleeding patients after cardiac surgery identified fewer reoperations for bleeding and decreased allogeneic blood transfusion rates in patients who received high and low dose of rFVIIa [58]. A recent meta-analysis of
35 randomized trials with 4,468 subjects has indicated that rates of venous thromboembolic events were similar for subjects who received rFVIIa compared with placebo; arterial events, however, were significantly higher in subjects receiving rFVIIa compared with placebo, particularly for older patients and/or higher doses, raising concerns regarding the safety of rFVIIa for management (or prophylaxis) of bleeding [59]. Use of eFVIIa should be guided by individual patient risk-benefit analysis, and with consideration of the potential risk factors.

- **Factor XIII:**

  FXIII plays an important role in coagulation, by cross-linking and stabilizing the newly formed clot, as well as protecting it against fibrinolysis. Acute FXIII deficiency is relatively common in surgical setting (usually because consumption), and may contribute to “unexplained” intraoperative bleeding. However, FXIII is not detected by PT and PTT and specific laboratory tests are needed to quantify it in plasma [60]. Some studies suggest that FXIII replacement is effective in reducing perioperative bleeding [61,62], but more studies are needed to better establish the efficacy of this treatment. Clinical trials on safety and efficacy of recombinant FXIII in reducing blood loss and transfusion rates in cardiac surgery are ongoing [63,64].
References:


13) Holland LL, Foster TM, Marlar RA & Brooks JP. Fresh frozen plasma is ineffective for correcting


