HOW DO I SELECT EVIDENCE-BASED TRANSFUSION THRESHOLDS FOR PLATELETS, PLASMA AND CRYOPRECIPITATE?

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There are limited data that provide guidelines for the transfusion of platelets, plasma and cryoprecipitated antihemophilic factor (cryo). In addition to this deficiency, the results of some studies have provided conflicting evidence, which may inadvertently contributed to prolonging this uncertainty. Traditionally, health care providers have chosen arbitrary ordering practices (i.e., two units of frozen plasma [FP]) that may lead to donor exposure without significant clinical benefit. There have also been changes in products that can contribute to these arbitrary ordering practices, such as the notable changing from six-pack whole-blood derived platelets to either apheresis platelets in plasma or additive solution and use of pathogen reduction technologies.

Platelet products are generally given to patients with thrombocytopenia both prophylactically and hemostatically. They are also used in massive transfusion protocols as platelet consumption can occur rapidly during massive hemorrhage. Furthermore, these platelet products are also given to patients with subdural hematomas being treated with antiplatelet therapies (i.e., clopidogrel). Recent studies, such as the Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Hemorrhage Associated With Antiplatelet Therapy (PATCH) trial, have shown that this approach may not be advantageous.[1]

Plasma is the liquid part of blood, which contains diverse and dynamic coagulation factors and is often used to supplement deficient factor levels in patients. However, doses have historically been low and have often resulted in patient under-dosing. Many studies have shown that a beneficial dose is weight-based.[2,3] Unfortunately, this is not always followed due to individual patient needs and the provider's lack of education about dosing. In addition, plasma is often used for the reversal of vitamin K antagonists, despite data showing little efficacy compared to more novel treatments, such as three- and four-factor prothrombin complex concentrates and phytonadione (vitamin K1) supplementation.

Cryo contains fibrinogen, Factor VIII, Factor XIII and Von Willebrand factor. Cryo is typically used for the treatment of acquired hypofibrinogenemia and dysfibrinogenemia and is produced from slow thawing of plasma at 4^0C and expressing the precipitate from the unit. Due to the low yield associated with a single unit of plasma, the cryo product is often pooled to increase efficacy. While there is an

accepted dose calculation for increasing fibrinogen to a specific increment, it is often underused. Historically, the best practice for standard product dosing consists of two units of 5-pool cryo.

Fibrinogen increment formula[4]

Dose, units = desired fibrinogen increment (mg/dL) x plasma volume (dL) / 250* mg (per unit)

Desired fibrinogen increment = goal fibrinogen – initial fibrinogen

Plasma volume = (1-hematocrit) x 70mL/kg x weight (kg)

*Average fibrinogen per unit.

PATIENT BLOOD MANAGEMENT

Patient blood management (PBM) is a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood, while promoting patient safety and empowerment.[5] By leveraging this scientific and methodological approach, patients have the potential to avoid unnecessary transfusions and be directed toward alternative modes of therapy that could be more appropriate or advantageous. The goal of PBM is not to safeguard blood products; rather, the objective is for health care providers to present the most efficacious treatment possible to address patient need.[6] While blood transfusion safety has improved since Karl Landsteiner's discovery of compatible and incompatible ABO blood groups in 1900, it is not without risks.[7,8] Although there is no true replacement for blood, there are alternative therapies that may prove more beneficial than simply providing donated blood or blood-derived products and can thereby serve as critical resources for health care providers.

PLATELETS

A typical unit of apheresis platelets should increase the recipient's platelet count by 30,000 -60,000/uL in a 70kg patient in the United States (US). It should be noted, that the US has a higher platelet yield requirement at 3.0×10^{11} platelets than most other countries. In comparison to apheresis platelets, whole-blood derived platelets, which are often pooled, are expected to raise the platelet count by 5,000 to 10,000/uL in a 70 kg patient per unit.[4,9] Therefore, different types of platelet treatments used in PBM can yield different end results.

Patients may not respond as expected to platelet transfusion, which is referred to as "platelet refractoriness." Platelet refractoriness is often multifactorial and requires research into the patient's condition. There are many causes of platelet refractoriness in both patients who are immune-mediated and non-immune-mediated.[4]

Immune	Non-Immune
HLA antibody	Splenomegaly
HPA antibody	Sepsis
ABO mismatch	Bleeding
	Use of heparin or amphotericin
	Vaso-occlusive vascular disease
	Fever

HLA – human leukocyte antigen, HPA-human platelet antigen

PROPHYLACTIC PLATELET TRANSFUSIONS

Platelet transfusions for patients who are thrombocytopenic may be done prophylactically to either prevent or reduce the severity of spontaneous patient bleeding. Although this is a common practice, results of various studies question the efficacy of prophylactic platelet transfusions.[10,11,12] In addition to questioning efficacy potential, there are conflicting data regarding the appropriate dosing levels needed for advantageous patient outcomes.

Previously, a platelet count of <20,000/uL was used as an action-response trigger limit to instigate a prophylactic platelet transfusion.[9,13] Four randomized control trials were executed to investigate comparable outcomes between this <20,000/uL trigger value and alternative potential thresholds. The studies concluded there was no statistically significant difference in potential hemorrhagic risk level when using a 10,000/uL trigger rather than the 20,000/uL. Slichter and Harker, as well as Gaydos, Freirich and Mantel, showed in their studies that spontaneous bleeding is unlikely to occur until the platelet count is ≤ 5,000/uL.[13,14,15] In the US and England, it is recommended to use the platelet count 10,000/uL for those who are chronically thrombocytopenic.[16] This includes those who are receiving chemotherapy or have bone marrow conditions such as myelodysplasia.

INVASIVE PROCEDURES

Vascular integrity is important in the setting of trauma and in surgery. To ensure patient safety in these situations, it is recommended that a platelet count of 50,000/uL is used as a standard for surgical procedures.[9, 16] However, different surgical procedures do pose different and unique risks; for example, patients undergoing neurosurgery may have an increased risk for significant adverse outcomes resulting from intracerebral bleeding. Due to the potential for adverse outcomes, the standard of care for patients undergoing neurosurgery or ophthalmologic surgery have a platelet count of >100,000/uL to ensure that a sufficient platelet surplus is in circulation to compensate for this potential risk. Regardless of guidelines, the patient's condition should always be taken into consideration when transfusing platelets. Important factors to take into consideration notably include the ability to control bleeding, bleeding risk (i.e., coagulopathy, both drug-induced and hereditary), platelet dysfunction and rate of hemorrhage.

ANTI-PLATELET THERAPY

With the aging population in many countries growing, there is an increase in the rate of vascular disease. This has led to a subsequent increase in the use of anti-platelet drug therapy, which poses a risk to patients experiencing bleeding. Notable anti-platelet drug therapy options include $P2Y_{12}$ inhibitors (i.e., clopidogrel), whose mechanism of action allows them to block the ADP receptors present on platelet bodies. Blocking the ADP receptor prevents both platelet aggregation and thromboxane generation. Aspirin, which is also an anti-platelet therapy, works by inactivating cyclooxygenase thereby down-regulating subsequent prostaglandin synthesis.[17] This includes the critical prostaglandin thromboxane A_2, which is necessary for hemostasis by increasing platelet aggregation and vasoconstriction. Despite the lack of persuasive clinical evidence, it nonetheless remains the standard recommendation that 1–2 apheresis platelets be given to reverse antiplatelet therapy in the bleeding patient.

PLASMA

Plasma is made by separating donated blood via centrifugation: as a function of centrifugal force, the erythrocytes travel to the bottom of the container, and the plasma matrix components are left at the top. The plasma and erythrocytes are separated by platelets and white blood cells. For plasma samples to be compliantly labeled as fresh frozen plasma (FFP), the plasma must be separated and frozen within eight hours of collection. Labels for plasma products frozen within 24-hours of collection are nomenclated as "PF24."[4, 17] Both products are considered clinically equivalent and comprise most of the plasma available for transfusion. However, there is a notable product called plasma frozen within 24 hours after phlebotomy held at room temperature for up to 24 hours (PF24RT24); this product has a 13% decrease in factor VIII (13%) and a 10% decrease in protein S in comparison to FFP, due to the delayed product freeze start time.[17]

Patient plasma dosing should be weight-dependent, which is generally defined as 10-20ml/kg. [17, 18, 19] Historically, there has been a lack of randomized controlled trials to guide plasma transfusion thresholds. Often, plasma is ordered to correct the prothrombin time/international normalized ratio (PT/INR) before an invasive procedure. This is done despite the lack of evidence to correlate the PT with patients' bleeding risk. Furthermore, plasma products have been used to correct anticoagulation events instigated by both drug-induced and native hereditary factors. For coagulopathies, such as hemophilia A or B, plasma transfusion should be avoided, except under emergent circumstances, as factor specific therapy is available. Plasma is also ordered as a part of the massive transfusion protocol.[4]

ELEVATED INR

An elevated INR is the most common indication for plasma transfusion. While there is no set guideline for an abnormal INR, an action-alert level of ≥1.5 or 2.0 is conventionally used by clinicians as a trigger for initiating a plasma transfusion.[17] Transfusion at INRs below 1.5 may not be clinically beneficial, as the INR in FFP can be as high as 1.3.[20, 21] As indicated above, this is often for patients who are about to undergo an invasive or surgical procedure with the potential risk for

an inadvertent bleeding event. To ensure both product efficacy and patient safety, the quantity of plasma products used in the transfusion procedure should be dependent on, and determined by, the patients' weight as opposed to external or arbitrary factors. Despite this being a common indication, there is a lack of evidence to support prophylactic plasma transfusion.[20, 22, 23, 24]

Patients with liver diseases or deficiencies are the exception to this INR indication. As most of the coagulation factors are synthesized in the liver, such patients can have depressed concentrations that subsequently lead to further complications. Liver disease and vitamin K deficiencies can cause K-dependent factors (Factors II, VII, IX, and X) to decrease.[17, 25, 26] In addition to decreased factor synthesis, advanced liver disease also results in the loss of anticoagulant factors antithrombin and proteins C and S. The loss of natural anticoagulants leads to rebalanced hemostasis.[27] The PT and INR measures the extrinsic coagulation system, which starts with Factor VII, making it a sensitive test for patients with liver disease who are progressing. However, this is misleading, as it only measures the decreased activity of these procoagulant factors; although these patients may appear to be coagulopathic, their coagulation system compensates by up-regulating in response to the decreased vitamin K-dependent factors. [26, 28]

VITAMIN K ANTAGONIST REVERSAL

Plasma has been used for the reversal of vitamin K antagonist drugs prior to surgery or in the presence of life-threatening bleeding. Currently, it is recommended to avoid plasma transfusion for the reversal of vitamin K antagonists, as it is unlikely to accurately or reliably correct the drug-induced coagulopathic event.[4,19,22] Furthermore, recent advances in PBM and clinical practices have resulted in additional options becoming available for use. As a medical practice, plasma products should only be used when prothrombin complex concentrates are unavailable and the patient is at risk. When plasma is used, it should be dosed at 20-25ml/kg in this patient population.[17] If the patient is stable and not at risk for comorbidities, anticoagulation reversal can be managed using phytonadione prior to the invasive procedure. Phytonadione, or Vitamin K1, can reverse vitamin K antagonists within four to six hours when given intravenously. Previously, Vitamin K was emulsified with polyoxyethylated castor oil which contributed to anaphylactic/anaphylactoid reactions. IV Vitamin K formulation has since been changed to polyoxyethylated fatty acid derivatives, which may decrease the risk for allergic reactions. Plasma, when dosed correctly, carries a higher risk for allergic reaction compared with IV vitamin K.[17] Perioperative management is very important with patients treated with vitamin K antagonists, since they can be managed without blood products in most routine scenarios.

CRYOPRECIPITATED ANTIHEMOPHILIC FACTOR

Data is lacking for transfusion indications or thresholds for the use of cryo. The most common uses for cryo are for hypofibrinogenemia in massive hemorrhaging patients. Results of more recent studies have shown that fibrinogen may be used as a marker for mortality in patients treated for trauma. These data suggest that a fibrinogen level of ≤150mg/dL are indicative of mortality risk associated with trauma. Early administration of fibrinogen or cryoprecipitate may decrease the risk of mortality. [29,30]

Due to the inherent constraints and limiting factors involved in the manufacturing process, little cryo material is produced per single unit of plasma. As a result, it is often reconstituted in plasma and then frozen (approx. 15 mL per unit). Since the volume is small, cryo can be pre-pooled at the blood center and provided to transfusion services as five or ten pool cryo. A single unit of cryo in the US must contain at least 150 mg of fibrinogen, but can range from 150-250 mg. The standard dose for an adult is ten pools of cryo, or two five pools. The ten pools should increase fibrinogen levels by 50-100 mg/dL.

COAGULATION ASSAYS

Traditional static coagulation assays may not accurately reflect a patient's risk for bleeding.[17, 21] The activated partial thromboplastin time and PT were developed to measure the degree of anticoagulation with heparin and vitamin K antagonists, respectively. Their use in clinical medicine to assess the degree of bleed risk has been incorrectly applied. The clinical situation should always be taken into consideration when using any coagulation assay to make medical decisions, such as transfusing blood products.

Viscoelastic testing (TEG/ROTEM) more accurately depicts hemostasis in vivo. Whole blood is used for these assays, and it measures platelet, fibrinogen, as well as factor contribution to clot formation. While viscoelastic testing does predict bleed risk more accurately than static coagulation assays, examining patient correlation is important when interpreting the results.

In addition to viscoelastic testing, platelet function assays are more readily available. These assays, such as the platelet mapping kit from TEG, may accurately measure platelet response to adenosine diphosphate and arachidonic acid. This measures the degree of dysfunction cause from $P2Y_{12}$ inhibitor and aspirin, respectively. This can be used to gauge whether a platelet transfusion is needed, since the drug may have cleared. It is also of note that approximately 30% of patients treated with $P2Y_{12}$ inhibitor are unaffected.

PLATELET COUNT

Post-transfusion platelet counts are needed to determine platelet refractoriness. This is important in managing both the patient, and the platelet supply. Following a repeated corrected count increment (CCI) 1 hour post transfusion of <7,500 is indicative of platelet refractoriness.[8] The clinician should then determine the cause of refractoriness. Immune-mediated causes may be mitigated by providing HLA-selected platelets or crossmatched platelets. Nonimmune causes should be managed by the clinician to avoid destruction and clearance of transfused platelets. An example of this is the administration of intravenous immune globulin in the setting of splenomegaly. CCI can only be used if the number of platelets transfused is listed on the container. Poor increments (e.g., <10,000/uL) on at least two post-transfusion counts may be attributable to immune refractoriness. [31]

Corrected count increment formula:

CCI = count increment (/uL) x BSA (m^2) / unit platelet yield

BSA – body surface area

CONCLUSION

Of the three products discussed, platelet transfusions have the highest amount of evidence for prophylactic transfusions. Prophylactic platelet transfusions are commonly used for oncology patients to maintain an adequate number of circulating platelets and prevent spontaneous hemorrhage. A platelet count of ≤10,000/uL has been traditionally used as an indication. Recent research shows that the risk for spontaneous bleeding is unlikely until the platelet count reached ≤5,000/uL. There is no current evidence in the support of prophylactic plasma or cryo transfusions.

Perioperative management of anticoagulated patients is essential. Discontinuing anticoagulants and antiplatelet therapy at an adequate time to allow sufficient metabolism and clearance before a procedure prevents unnecessary transfusion of plasma and platelet products. Platelet-mapping assays can be used to assess the inhibition of platelets in vivo, and traditional static coagulation testing can monitor patients on most anticoagulants. Emergency cases are an exception to perioperative management, since they are typically unpredictable.

When transfusing plasma using an INR, the patient's clinical condition should be taken into consideration. Patients with liver disease may have an abnormal INR but remain hemostatically stable. Additional coagulation testing should be taken into consideration to prevent exposing a patient to a blood product with limited clinical benefit, as there have been cases of mortality associated with unnecessary plasma transfusion through immune mediated transfusion reactions (i.e., transfusion-related acute lung injury).

Data remain limited for the transfusion of cryo. It is mainly used to increase fibrinogen, since low levels of fibrinogen have been correlated to mortality in patients treated for trauma. Thrombin generation assays as well as viscoelastic testing are useful in guiding cryo transfusion. Cryo also contains platelet microparticles, which are thought to have a procoagulant effect on circulating platelets. Cryo can be dosed based upon the desired fibrinogen increase and current fibrinogen level, preventing under and over-transfusion of the product.

Selecting evidence-based transfusion criteria for 'all things yellow' (platelets, plasma, and cryo) is a multifaceted task. The common indication for transfusion is to either maintain hemostasis, or to correct a hemostatic abnormality. Not every patient presents the same, nor do they bleed the same. The patient's clinical condition must be taken into consideration when transfusing platelets, plasma or cryo. This includes any genetic deficiencies affecting the coagulation system. It is also worth mentioning that patients should not be transfused based on coagulation testing alone. Coagulation testing, whether it be a static coagulation assay or viscoelastic testing, should be correlated with the patient's clinical condition and risk for hemorrhage.

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