UPDATE ON PLATELETS

Preparation and Administration

Platelets can be prepared as random-donor platelet concentrates from whole blood derived platelets or as apheresis platelets from a single donor. In the whole blood harvest method, 500 mL of blood is collected and stored in a citrate preservative at room temperature.[i] Within eight hours, the blood is centrifuged with a slow spin and the platelet-rich plasma (PRP) is separated into an attached empty satellite bag. This PRP is centrifuged again with a fast spin and separated into one unit of platelet concentrate and one unit of plasma. Each unit of platelets contains 5.5×10^{10} platelets in 50 to 70 mL of plasma (to maintain the pH at >6.2) and 4 to 10 units of platelets are usually pooled together in a single component bag.

Alternatively, platelets can be isolated from whole blood from the buffy coat layer, following centrifugation of whole blood in specific bags that removes RBC and plasma through tubings in the bottom and top of the bag. The platelet-enriched buffy coat is further processed (through centrifugation and/or leuko-reduction filters) to eliminate WBCs and remaining RBCs. This method is currently employed in Europe and Canada and it permits storage of whole blood at room temperature for up to 24 hours prior to platelet harvesting and provides some other potential advantages.

Apheresis platelets, or single donor platelets are obtained by performing apheresis on volunteer donors. During this procedure, large volumes of whole blood are processed into an extracorporeal circuit and centrifuged to separate the components. The red blood cells and a certain percentage of the plasma are returned to the donor. A single donor on apheresis donates the equivalent of $> 3.0 \times 10^{11}$ or six units of whole blood derived platelets suspended in a volume of 200 to 400 mL of plasma.

Single donor pheresis-derived platelets minimize the number of donor exposures for the transfusion recipient and have become the primary source of platelets in the US.[i]

Platelets should be stored at room temperature (20º to 24ºC) for up to five days with continuous gentle agitation to facilitate gas exchange and prevent platelet aggregate formation. The American College of Pathologists and the American Association of Blood Banks mandate that all platelet products be tested for bacterial contamination prior to transfusion. The administration of ABO-specific platelets is not strictly (i.e., usually limited to 300-500 mL of out-of-group plasma) required because platelet concentrates contain few red blood cells. However, administration of non-ABO specific platelets may be of concern with transfusion of pediatric patients with a small blood volume because of anti-A and/or anti-B in the plasma. The administration of out-of-group pooled platelet components leads to passively acquired anti-A and/or anti-B, and may cause a weakly positive direct antiglobulin test in the recipient due to anti-A and or anti-B present in the donor plasma. Platelets made from Rh positive donors are often transfused to Rh negative patients because of the scarcity of platelets made from Rh negative individuals. Although there are minimal numbers of red cells in platelets, those Rh negative women of child-bearing age or younger who receive Rh positive platelets might be given consideration for RhIG to prevent anti-D formation and the possibility of future hemolytic disease of the newborn.

As for all blood products, platelets must be infused through a standard filter which can be found in either a platelet or standard component administration set, which contains a 170-260 micron filter. Microaggregate filters (20-micron to 40-micron) should not be used because they will remove most of the platelets. Most blood centers can provide leukoreduced apheresed platelets because the apheresis machines can provide a product with less than 5×10^6 white blood cells. Whole blood derived platelets are often not leukoreduced. Extreme warming of platelets (>43-45 degrees C) has been shown to impair platelet aggregation and to alter cytoskeletal membrane components.[ii,iii]

Manufacturers of fluid warming devices generally do not recommend infusing platelets through such a device, although data are scarce that would suggest that infusion through these warming devices is detrimental to platelet function.

Evidence-Based Indications for Platelet Therapy:

Prophylactic Platelet Transfusion

The majority of prophylactic platelet transfusions are given to patients with severe thrombocytopenia surgical and non-surgical settings. Most data suggest that prophylactic platelet transfusions should be given to non-surgical patients with chronic thrombocytopenia when counts are below 10,000 and in the face of active bleeding. Spontaneous bleeding due to thrombocytopenia alone does not occur until the platelet count is below 10,000 plts/µL. The question of the appropriate platelet trigger for a prophylactic transfusion has yet to be answered. In the past, 20,000 platelets/µL was used, however a review of trials comparing 10,000/µL vs. 20,000/µL as the trigger revealed no difference in efficacy and a cost savings when 10,000/µL was used as the trigger. [iv,] The prophylactic administration of platelets is not recommended in patients with heparin-induced thrombocytopenia or with chronic thrombocytopenia caused by increased platelet destruction (e.g., idiopathic thrombocytopenic purpura). In fact, transfusion may be ineffective due to refractoriness in a substantial percentage of these patients.[v,vi,vii,viii]

Therapeutic platelet transfusions are usually indicated in the non-surgical arena when bleeding reaches the WHO grade 2 level (evidence of hemorrhage not requiring excess red cell transfusions).[ix]

Perioperative Indications

Despite paucity of evidence, recommendations (not strict indications) for platelet transfusion are to some extent arbitrary and change as more data emerge. When invasive procedures are performed,

platelet transfusion is generally prescribed to raise the platelet count to levels of 50 x 10^9/L or to treat a known platelet function defect. This is not necessarily the case for minimally invasive procedures (central line placement, angiography, thoracentesis, and paracentresis), where a platelet count of 30,000 or less may be adequate.[x] One unit of apheresis platelets or a pool of 4 to 6 whole blood-platelets increases the platelet count by approximately 30-50 x 10^9/L in the average adult. For pediatric patients a dose of 10 ml/kg or one unit of platelets/10 kg will generally increase the platelet count to adequate levels.[xi] In critically ill patients, platelet transfusion may increase the platelet count in 50% of recipients which introduces the question of whether "responders" demonstrate more effective platelet contribution to clot formation than "non-responders". Surgical and obstetrical patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 x 10^9/L and rarely require therapy if it is greater than 100 x 10^9/L.[iii] There is a paucity of data suggesting a "safe" platelet count for placement of an epidural catheter in the obstetric patient. In obstetric patients with von Willebrand disease, idiopathic thrombocytopenic purpura, and hemophilia, safe neuraxial anesthetics have been conducted with platelet counts ranging from less than 50 x 10^9/L to greater than 100x 10^9/L, and complications have not been directly linked to platelet count. In patients undergoing cardiac surgery, platelet transfusion is often the first line treatment for excessive post-operative bleeding with no identifiable surgical source since platelet dysfunction is common after cardiopulmonary bypass.[xii] Factors to consider for the transfusion of platelets for counts between 50-100 x 10^9/L are the type of surgery, extent of actual blood loss or microvascular bleeding, presence of potent antiplatelet medications and disorders like uremia that are known to affect platelet function and coagulation. In patients sustaining trauma and hemorrhagic shock, some retrospective studies have demonstrated a survival advantage with increased platelet:red blood cell transfusion ratios using a massive transfusion protocol.[xiii] (see current COBM MTP document) Surgery within a closed space such as in neurosurgery usually requires that the platelet

count be increased to 100 x 10^9/L in order to ensure adequate hemostasis.[vii,xiv] Operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50 x 10^9/L.[iii] Furthermore, platelet count alone does not provide an assessment of platelet function and platelet transfusion may be necessary if microvascular bleeding persists despite a normal (>100 x 10^9/L) platelet count.[iii] Patients with congenital platelet disorders and/or those with a recent history of taking aspirin, clopidogrel, prasugrel, or having been treated with a glycoprotein IIb/IIIa receptor antagonist will have various degrees of platelet dysfunction and should have platelet function measured. The responsiveness to platelet transfusion depends upon the type of platelet defect, the reversibility of the drug administered, and the timing of the last dose of anti-platelet drug.[xv] Various herbal compounds such as Ginkgo biloba, Asian ginseng, St. John's wort, and saw palmetto may also interfere with platelet function.[xvi]

Platelet Function Testing

Qualitative platelet function testing has become much more sophisticated as a result of the increased use of anti-thrombotic drug therapy. In treating surgical or perioperative bleeding, the viscoelastic tests such as the thromboelastograph (TEG®), Sonoclot®, and the ROTEM® have been used to assess platelet function and determine transfusion needs. The surgical arenas in which these tests have been most extensively studied include trauma, cardiac surgery, obstetrical hemorrhage, and liver transplantation.[xvii,xviii,xix,xx]

Anti-Platelet Therapy- Perioperative Management

The prevalence of drug-eluting stent therapy and resultant use of dual anti-platelet therapy has sparked enormous interest in the management of patients receiving such therapy when they present for surgery. The evidence-based ACC/AHA Guideline for percutaneous coronary interventions (PCI) states that dual anti-platelet therapy should be maintained for at least one year, yet it has been shown that these patients have an increased risk of bleeding. If 12 months have passed since the time of PCI, best medical judgment decisions are made regarding whether one or both anti-platelet agents should be discontinued, and for how many days, before surgery.[xxi] These decisions take into account the risk of recurrent ischemia, the coronary anatomy, the surgical procedure, and the patient's overall risk for bleeding. STS/SCA Guidelines for cardiac surgery recommend discontinuation of thienopyridine anti-platelet drug therapy before cardiac surgery as a Class IB recommendation.[xxii] The time period for discontinuation is to be dependent on the drug pharmacokinetics and the patient risk and this guideline acknowledges that 3 days drug discontinuation may be prudent for coronary protection. The American College of Chest Physicians published guideline recommends that clopidogrel be discontinued for 5 days before surgery in patients at high risk for cardiac events, and for 7-10 days in patients at low risk.[xxiii] This recommendation has been supported by the ASA. If possible, aspirin should be continued throughout this period. Within 12 months of PCI, it is generally considered a risk for coronary ischemia to stop one or both anti-platelet agents before surgery. Careful analysis, platelet function testing, and bridging therapy have all been employed but without much guidance from the literature. For specific platelet-function testing, agonist-specific assays should be employed (TEG-Platelet Mapping, Multiplate, VerifyNow; Table 1) There has been some clinical evidence to support the predictive value of platelet function testing for coronary stent thrombosis[xxiv] in patients with coronary artery disease but these data are not conclusively predictive.

However, platelet function testing to predict perioperative bleeding and the need for transfusion may be useful. Additional clinical studies to determine cut-off values for bleeding or thrombosis risk are needed.

Risks of Platelet Transfusion

Adverse reactions to platelet transfusion may present as nonhemolytic febrile reactions (incidence 1:20) or mild allergic reactions (1:100). Major complications associated with platelet concentrate administration include transfusion-related acute lung injury (TRALI), transfusion-transmitted infections/transfusion-associated sepsis, and allergic reactions.[xxv,xxvi] TRALI remains the leading cause of transfusion-related fatalities reported to the FDA.[xxvii] According to data collected from the American Red Cross in 2008, the risk of TRALI per component transfused was greater for apheresis platelet concentrate transfusions than any other blood component therapy (estimated at 15.7 cases per 10^6 components transfused).[xxviii] While the per component risk of TRALI for whole-blood derived platelet concentrates is believed to be less than the risk for apheresis platelet components,[xxix] this assertion remains a subject of debate.

As with all blood component therapies, the risk for transfusion transmitted infections remains a concern. However, the rates of viral transmission (e.g. HIV, HBV, HCV) are exceedingly low. A specific concern with platelet concentrate transfusion is transfusion-associated sepsis (TAS) with bacterial contamination of platelets being the third leading cause of transfusion-related mortality. Storage of platelets at room temperature provides a favorable environment for bacterial contamination with resultant septic transfusion.[xxx] Platelet transfusion currently represents the *largest overall infectious risk* in our blood supply. This risk appears to increase with the duration of platelet storage and is greater with whole-blood derived platelets products procured from multiple donors than it is for apheresis platelet concentrates procured from a single donor.[xxxi] Notably, while

more effective microbial testing strategies have reduced the rate of this complication, substantial false negative testing rates persist. Testing for bacterial contamination of platelets is available and will continue to be a critically important issue. As these tests become more accurate, increased numbers of blood banks will be implementing them in order to minimize infectious risk. Febrile non-hemolytic transfusion reactions and allergic reactions are also more common with platelet concentrate transfusions when compared to other blood component therapies. In part, this is again believed due to the requirement for room temperature storage conditions.

In addition to the complications noted above, there is a decreased responsiveness to platelet transfusion manifesting in reduced number augmentation and reduced longevity that occurs as the number of transfusions increases and if ABO-incompatible platelets are given. Alloimmunization can also occur in platelet transfusion since platelets express A and B red blood cell antigens, HLA antigens, and platelet specific antigents, and can elicit a host immune response.[xxxii,xxxiii] This immune response is not only a reaction to A and B antigens but also stimulates the overall immune system and can cause other alloantibodies to be made. After multiple doses, platelet transfusion may result in an immune platelet refractory state and/or difficulty in finding a future potential solid organ or bone marrow transplant donor. It should be noted that the HLA sensitization is due more to the white cells found in the platelet product than to the platelets themselves. In addition to leading to platelet transfusion refractoriness, these platelet alloantibodies have been implicated in the occurrence of a rare complication of transfusion therapy termed post-transfusion purpura.[xxxiv] Investigators have sought an association of platelet transfusion with adverse outcomes, but this relationship has not been demonstrated in randomized or large scale observational trials.[xxxv]

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