

Platelet transfusions: trigger, dose, benefits, and risks

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Abstract

Over the last half century, platelet transfusion has been an effective therapy for the prevention and treatment of bleeding, particularly in patients with hematologic malignancies. Recent randomized trials have demonstrated that current practices may be suboptimal in a number of ways. The rationale for parsimony in the use of this powerful therapy includes previously described severe and fatal adverse outcomes (including refractoriness, hemolysis from ABO-mismatched transfusions, acute lung injury, and bacterial sepsis), newly described serious potential risks (including thrombosis and earlier leukemic recurrence), difficulty in maintaining adequate supplies of platelets, the need to place volunteer donors on cell separators to provide the product, and cost. Recent findings demonstrate that the platelet count threshold for prophylactic transfusion can be as low as 10,000/ μ L, and a therapeutic rather than a prophylactic strategy of transfusion for bleeding manifestations only may be equally safe for most patients. Another recently completed study suggests that very low doses of platelet transfusions (the equivalent of half a unit of apheresis platelets or two to three units of whole blood-derived platelets) are as effective at preventing bleeding as much higher doses. One question for which there are no randomized trial data is at what threshold prophylactic platelet transfusion should be given before invasive procedures or major surgery. The typically recommended threshold of 50,000/ μ L is based only on expert opinion, and substantial observational data indicate that this threshold leads to many transfusions that are likely unnecessary and therefore represent risk with little or no additional benefit.

Introduction and context

Source, dose, benefits, risks, and prophylactic transfusion triggers

The goal of platelet transfusion is to stop or prevent bleeding in thrombocytopenic patients or those with platelet dysfunction [1-3]. Bleeding is a relatively uncommon cause of death in non-trauma patients but can be a significant morbid event at worst and, at best, quite upsetting for patients, families, and providers. Thus, traditionally, with the view that platelet transfusion is essentially benign, the impetus has been to transfuse platelets aggressively to prevent rather than treat bleeding. There are two types of platelet products for transfusion. Whole blood platelets, which are derived from four to five whole blood

donations, pooled, leukoreduced, bacterially tested, and irradiated, used to be the standard transfusion product but now are less frequently used in the US. Apheresis platelets derived from donors who spend a couple of hours on a cell separator have become the most commonly used product in the US. The usual doses have been in the range of 3×10^{11} to 5×10^{11} platelets per transfusion but one-quarter to one-half of these doses has been shown to be equivalent in preventing bleeding in a recent but as yet unpublished large national randomized trial (Prophylactic Platelet Dose on Transfusion Outcomes, or PLADO) [4]. Whole blood pooled and apheresis platelets are considered by most experts to be interchangeable in terms of efficacy and safety.

Risks

Patients receiving pheresis platelets are likely to have a higher risk of hemolytic reactions if they are ABO-mismatched [5-7] and a higher risk of acute lung injury (transfusion-related acute lung injury) due to having larger amounts of plasma from a single donor, but carry a lower risk of infectious disease transmission due to fewer donor exposures. Earlier studies have demonstrated that alloimmunization and refractoriness to transfusion (inability to raise the platelet count with transfusion) are common in recipients of non-leukoreduced transfusions [8] and ABO-mismatched platelet transfusions [9]. Thus, almost everyone agrees that platelet transfusions should always be leukoreduced and that every effort should be made to use only ABO-identical platelets whenever possible.

For patients who have severe or repeated fever, rigors, or allergic or pulmonary complications with transfusion (about 1-5% of patients; mostly fever, rigors, and/or urticaria), saline-washed platelets are available in some hospitals [10]. These require about 2 hours of additional preparation time and contain about 20% fewer platelets than unwashed platelets. One study suggests that clinical outcomes (survival) are improved with the use of washed platelets in adult patients with acute leukemia and that post-transfusion fever, rigors, and urticaria can be almost completely eliminated [11].

Indications

Traditionally, platelet transfusions in hematology-oncology have been given prophylactically as serious bleeding is fortunately uncommon in these patients. The safe threshold for prophylactic transfusion in a clinically stable patient who does not have serious bleeding (e.g., that requiring red cell transfusion or representing serious or life-threatening morbidity) is considered to be a platelet count of 10,000/ μ L [12-14]. There is reasonable consensus that for patients who are bleeding, septic, or hemodynamically unstable, the threshold for transfusion should be raised to 15,000-20,000/ μ L. Patients with life-threatening bleeding in the chest or head are usually transfused at higher platelet count thresholds (30,000-50,000/ μ L). Despite the evidence that a platelet count of more than 10,000/ μ L is adequate to prevent spontaneous hemorrhage and that serious bleeding is quite rare at counts above 20,000/ μ L, many interventionalists and surgeons nonetheless insist on platelet counts of at least 25,000/ μ L for multi-lumen catheter insertion and 50,000/ μ L for invasive procedures such as major surgery or liver or lung biopsy. The evidence in support of these practices is nil, but traditional practices do not change without convincing evidence demonstrating that they are unnecessary or even counterproductive, and these practices may well be both.

An uncommon indication for platelet transfusion is a platelet dysfunction (due to disease or a commonly employed drug such as aspirin) that is associated with serious bleeding or that accompanies the need for major surgery or another high-risk invasive procedure such as liver biopsy.

One reason that strategies for platelet transfusion have been difficult to study and change is that the effectiveness of platelet transfusion is not easily evaluated. If the transfusion is therapeutic, then the amount and rate of bleeding are the only really important measures of response. Quantitation of these is not easily achieved. There are no laboratory tests that adequately measure the efficacy of platelet transfusion, thus clinical evaluation is the only appropriate approach. In the case of prophylactic platelet transfusions, the situation is even more difficult. The increase in platelet count is the only available response measure other than the absence of bleeding. The general goal has been to achieve a platelet count above 20,000/ μ L, but the post-transfusion platelet count is usually not measured except in hematology-oncology patients and, in any case, platelet count correlates very poorly with bleeding. Typically, platelet counts are performed each morning and if the count is below 10,000/ μ L, a platelet transfusion is given. In patients with bleeding or requiring invasive procedures, post-transfusion platelet counts can be performed at any time after the transfusion, from a few minutes to a few hours. Because increments are often transient in acutely ill patients, the transfusion should be performed just prior to any invasive procedure, not the day before or several hours before. A common practice, albeit one based on common sense rather than data, is to infuse platelets during the procedure to ensure that additional platelets are present during the time of maximal challenge to hemostasis.

Platelet transfusion refractoriness

If refractoriness to platelet transfusion (poor post-transfusion platelet count increments) is suspected, this is evaluated primarily by immediate post-transfusion count increments (approximately 10-60 minutes after completion of the transfusion). HLA antibody-mediated immune refractoriness is further differentiated from other causes such as sepsis, hypersplenism, and drug-related causes by measurement of anti-platelet/anti-HLA antibodies and failure to raise the platelet count post-transfusion. In other causes, there is often a short-lived (a few hours) rise in count but poor platelet survival post-transfusion. The most common cause of severe refractoriness is allosensitization, the formation of IgG antibodies to HLA-A,B (class I major histocompatibility complex) antigens in the transfusion recipient due to

prior pregnancy or transfusion or both. Donor alloimmunization to HLA class I and II or granulocyte antigens (i.e., antibody in the platelet product) can be an etiology for transfusion-related acute lung injury in the recipient. Recipient alloimmunization to HLA class I in previous non-sensitized patients is almost entirely prevented by using leukoreduced red cells from which the platelets and white cells have been removed by filtration and leukoreduced platelets from which the white cells have been removed [8]. Universal leukoreduction is standard procedure at almost all European hospitals. Unfortunately, not all hospitals in the US practice universal leukoreduction of blood components, thus patients may come to referral centers with recent prior transfusion sensitization. Women, particularly those with multiple pregnancies, are more likely to experience this complication than men are. Unfortunately, once refractoriness has developed, it portends a poor overall prognosis [15].

In the refractory patient, anti-HLA class I antibody tests using panel reactivity that employs a cytotoxicity method are often used. An enzyme-linked immunosorbent assay or immunofluorescent assay that detects anti-platelet-specific antibodies (very rare) and HLA class I antibodies is also used in some instances. If specificities can be determined, selecting platelet donors who lack the class I HLA antigens to which the recipient has antibody is the simplest and fastest approach to dealing with immune refractoriness. Two other strategies have some success: HLA-A,B-matched platelets and crossmatched platelets. Both strategies have a good but not great success rate of about 50-75% if a grade A or B HLA match or crossmatched platelet apheresis unit is available. A grade A or B HLA match is when the donor platelets carry no HLA-A,B antigens that are not identical with or serologically cross-reactive with those of the recipient. Sometimes, a family member, particularly an HLA-matched sibling who served as the donor for a stem cell transplant, can be the best donor as they tend to be closely matched. Many cases of clinical refractoriness currently are due to drug-related anti-platelet antibodies, with common offending drugs being vancomycin, amphotericin, and other anti-microbials (rarely quinidine or other drugs). Tests for drug-related antibodies are not routinely available, and the primary approach is discontinuing the drug and observing whether transfusion responsiveness returns within a few days to a week of continuing platelet transfusion.

Recent advances

Recent data suggest the efficacy and safety of transfusing fewer and lower doses of platelet transfusions. The clearest indication for platelet transfusion is the presence of serious bleeding in the setting of severe

thrombocytopenia or platelet dysfunction. A strategy of transfusing only those patients with evidence of bleeding is called a therapeutic as opposed to a prophylactic strategy. This was supported by a recent randomized trial, and a larger trial is currently under way in the UK [16]. The evidence is that this strategy leads to fewer transfusions and no greater incidence of serious bleeding than a prophylactic strategy. There is obviously more minor bleeding (petechia, purpura, mild epistaxis, and so on).

Current opinion is moving toward a therapeutic rather than a prophylactic strategy as practitioners become more comfortable in foregoing transfusions in asymptomatic thrombocytopenic patients with ever lower platelet counts. The potential advantage is that platelet transfusion is far from benign, being associated in recent studies with multi-organ failure [17], acute lung injury [18], bacterial sepsis [19,20], and even earlier recurrence of leukemia [21]. Platelets are clearly an important component of the innate immune system, perhaps explaining their postulated pro-inflammatory [22] and pro-thrombotic effects after storage and transfusion [23].

Preliminary studies raise the possibility that ABO-mismatched platelet and plasma transfusions predispose the patient to bleeding and mortality [24]. Recent reports suggest that platelet transfusions are immunomodulatory, pro-inflammatory, and pro-thrombotic [21,25-28]. With increasing evidence of previously undetected serious and even life-threatening effects of platelet transfusion, an enthusiastically prophylactic approach to transfusion is less and less attractive and indeed was never evidence-based in origin.

Implications for clinical practice

Prophylactic platelet transfusions need not be given for counts above 10,000/ μ L or prior to many invasive procedures for counts above 25,000/ μ L. Therapeutic platelet transfusions for bleeding are usually effective if the count can be raised above 20,000-30,000/ μ L, although many experts continue to advocate a threshold of at least 50,000/ μ L for major surgery and even at least 100,000/ μ L for some surgeries. There are no data supporting these numbers but this is the standard of practice and what is found in textbooks. The Society for Interventional Radiology specifies 25,000/ μ L platelets as the transfusion threshold for tunneled catheters but some physicians request even higher counts (unpublished Annual Meeting syllabi). Liver biopsy and other major procedures require thresholds of 50,000/ μ L but there is little or no evidence to suggest that this is optimal practice. Achieving these thresholds in acutely ill patients is often difficult and sometimes impossible.

Our advice is to give one platelet transfusion and if the count is still suboptimal, determine whether the radiologist, surgeon, or anesthesiologist will accept platelets transfusing during the procedure as an alternative to multiple boluses of platelets in a vain attempt to achieve an arbitrary number. There are a number of cases in our institutions in which infusion of three to seven doses of platelets has been associated with multi-organ failure after surgery, and there are similar reports in the literature. Platelet transfusions are likely pro-thrombotic and pro-inflammatory, and transfused platelets are highly activated [21]. There are very few or no situations, in our view, in which a second or third platelet transfusion will accomplish what a single platelet transfusion cannot. Platelet transfusion should not be considered benign and should be withheld unless there are compelling clinical indications, and these usually involve current serious bleeding accompanied by thrombocytopenia below 50,000/ μ L or platelet dysfunction. Serious bleeding is almost never explained primarily by thrombocytopenia with a platelet count that is between 50,000 and 100,000/ μ L in our clinical experience.

Competing interests

NB and JM have served as consultants to manufacturers of leukoreduction filters or products to reduce bleeding, including Pall Corporation (Port Washington, NY, USA), Fenwal Blood Technologies, Inc. (Lake Zurich, IL, USA), CaridianBCT (Lakewood, CO, USA), and Bayer (Leverkusen, Germany).

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References

- Brand A, Novotny V, Tomson B: **Platelet transfusion therapy: from 1973 to 2005.** *Hum Immunol* 2006, **67**:413-8.
 - Slichter SJ: **Platelet transfusion therapy.** *Hematol Oncol Clin North Am* 2007, **21**:697-729, vii.
 - Heal JM, Blumberg N: **Optimizing platelet transfusion therapy.** *Blood Rev* 2004, **18**:149-65.
 - Slichter SJ: **Background, rationale, and design of a clinical trial to assess the effects of platelet dose on bleeding risk in thrombocytopenic patients.** *J Clin Apher* 2006, **21**:78-84.
 - Sadani DT, Urbaniak SJ, Bruce M, Tighe JE: **Repeat ABO-incompatible platelet transfusions leading to haemolytic transfusion reaction.** *Transfus Med* 2006, **16**:375-9.
- F1000 Factor 3.0 Recommended
Evaluated by Neil Blumberg 09 Nov 2006
- Sapatnekar S, Sharma G, Downes KA, Wiersma S, McGrath C, Yomtovian R: **Acute hemolytic transfusion reaction in a pediatric patient following transfusion of apheresis platelets.** *J Clin Apher* 2005, **20**:225-9.
- F1000 Factor 3.0 Recommended
Evaluated by Neil Blumberg 04 Jan 2006
- Josephson CD, Mullis NC, Van Demark C, Hillyer CD: **Significant numbers of apheresis-derived group O platelet units have "high-titer" anti-A/A,B: implications for transfusion policy.** *Transfusion* 2004, **44**:805-8.
 - The Trial to Reduce Alloimmunization to Platelets Study Group: **Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions.** *N Engl J Med* 1997, **337**:1861-9.
 - Heal JM, Rowe JM, McMican A, Masel D, Finke C, Blumberg N: **The role of ABO matching in platelet transfusion.** *Eur J Haematol* 1993, **50**:110-7.
 - Vo TD, Cowles J, Heal JM, Blumberg N: **Platelet washing to prevent recurrent febrile reactions to leucocyte-reduced transfusions.** *Transfus Med* 2001, **11**:45-7.
 - Blumberg N, Heal JM, Rowe JM: **A randomized trial of washed red blood cell and platelet transfusions in adult acute leukemia [ISRCTN76536440].** *BMC Blood Disord* 2004, **4**:6.
 - Lawrence JB, Yomtovian RA, Hammons T, Masarik SR, Chongkolwatana V, Creger RJ, Manka A, Lazarus HM: **Lowering the prophylactic platelet transfusion threshold: A prospective analysis.** *Leuk Lymphoma* 2001, **41**:67-76.
 - Rebulla P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, Barbui T, Mandelli F, Sirchia G: **The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto.** *N Engl J Med* 1997, **337**:1870-5.
 - Wandt H, Frank M, Ehninger G, Schneider C, Brack N, Daoud A, Fackler-Schwalbe I, Fischer J, Gäckle R, Geer T, Harms P, Löffler B, Ohl S, Otremba B, Raab M, Schönrock-Nabulsi P, Strobel G, Winter R, Link H: **Safety and cost effectiveness of a $10 \times 10^9/l$ trigger for prophylactic platelet transfusions compared with the traditional $20 \times 10^9/l$ trigger - a prospective comparative trial in 105 patients with acute myeloid leukemia.** *Blood* 1998, **91**:3601-6.
 - Kerkhoffs JL, Eikenboom JC, van de Watering LM, van Wordragen-Vlaswinkel RJ, Wijermans PW, Brand A: **The clinical impact of platelet refractoriness: correlation with bleeding and survival.** *Transfusion* 2008, **48**:1959-65.
 - Wandt H, Schaefer-Eckart K, Frank M, Birkmann J, Wilhelm M: **A therapeutic platelet transfusion strategy is safe and feasible in patients after autologous peripheral blood stem cell transplantation.** *Bone Marrow Transplant* 2006, **37**:387-92.
- F1000 Factor 3.0 Recommended
Evaluated by Mike Murphy 24 Jan 2007
- Spieß BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, Murkin J, Nadel A: **Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes.** *Transfusion* 2004, **44**:1143-8.
 - Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ: **Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury.** *Anesth Analg* 2009, **108**:1083-91.
- F1000 Factor 3.0 Recommended
Evaluated by Marc De Kock 21 May 2009
- Rogers MA, Blumberg N, Heal JM, Hicks GL Jr: **Increased risk of infection and mortality in women after cardiac surgery related to allogeneic blood transfusion.** *J Womens Health (Larchmt)* 2007, **16**:1412-20.
 - Brecher ME, Means N, Jere CS, Heath D, Rothenberg S, Stutzman LC: **Evaluation of an automated culture system for detecting bacterial contamination of platelets: an analysis with 15 contaminating organisms.** *Transfusion* 2001, **41**:477-82.

21. Blumberg N, Spinelli SL, Francis CW, Taubman MB, Phipps RP: **The platelet as an immune cell-CD40 ligand and transfusion immunomodulation.** *Immunol Res* 2009, [Epub ahead of print].
22. McMorran BJ, Marshall VM, de Graaf C, Drysdale KE, Shabbar M, Smyth GK, Corbin JE, Alexander WS, Foote SJ: **Platelets kill intraerythrocytic malarial parasites and mediate survival to infection.** *Science* 2009, **323**:797-800.

F1000 Factor 3.0 Recommended
Evaluated by Charles Newton 27 Feb 2009
23. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH: **Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer.** *Arch Intern Med* 2008, **168**:2377-81.
24. Heal JM, Liesveld JL, Phillips GL, Blumberg N: **What would Karl Landsteiner do? The ABO blood group and stem cell transplantation.** *Bone Marrow Transplant* 2005, **36**:747-55.
25. Wagner DD: **New links between inflammation and thrombosis.** *Arterioscler Thromb Vasc Biol* 2005, **25**:1321-4.
26. Blumberg N, Gettings KF, Turner C, Heal JM, Phipps RP: **An association of soluble CD40 ligand (CD154) with adverse reactions to platelet transfusions.** *Transfusion* 2006, **46**:1813-21.
27. Cognasse F, Boussoulade F, Chavarin P, Acquart S, Fabrigli P, Lamy B, Garraud O: **Release of potential immunomodulatory factors during platelet storage.** *Transfusion* 2006, **46**:1184-9.
28. Sprague DL, Elzey BD, Crist SA, Waldschmidt TJ, Jensen RJ, Ratliff TL: **Platelet-mediated modulation of adaptive immunity: unique delivery of CD154 signal by platelet-derived membrane vesicles.** *Blood* 2008, **111**:5028-36.