Platelet Transfusions are Related to Adverse Outcomes

Pro:

Bruce D. Spiess, MD, FAHA
Professor of Anesthesiology and Emergency Medicine
Director of VCURES
VCUMC
Richmond, Virginia

Platelets are controllers of cellular coagulation function and are therefore necessary for coagulation after heart surgery. Consumption and dysfunction of platelets are the hallmarks of cardiopulmonary bypass leading to, at times, unpredictable post-operative hemorrhage. Recent widespread utilization of drugs inhibiting platelet adhesion and up regulation (plavix and aspirin) either alone or together has created even more anxiety about post-operative bleeding. This coupled with the near complete withdrawal of aprotinin as an effective agent to decrease bleeding has lead to pressure to utilize platelet transfusions. Platelet function is a widely utilized but poorly understood term. Indeed, platelets have hundreds of functions and many different ways to become stimulated to participate in the coagulation process (not just ADP and thromboxane). Monitoring platelet function with TEG’s, Sonoclots, Accumetrics (Verify Now) and PFA-100’s are not universal and even when utilized each of these tests has areas of platelet function that is left uncovered. In hospitals where such tests are readily and rapidly available there still exists some pressure to utilize platelet transfusions when unexplained bleeding occurs or when the anxiety about drug interactions is very high. The “Guidelines” for transfusion in heart surgery recommends using platelet function analysis as well as algorithm driven coagulation interventions along with limiting the use of platelet transfusion.

Platelets are metabolically active cells produced by megakaryocytes in the bone marrow. When activated they express a wide number of glycoprotein binding sites, spread and become amoeboid in shape. Eventually with enough stimulation they discharge their internal granules and undergo an irreversible activation such that they cannot recover. Platelets are harvested by centrifugation either immediately after whole blood harvest in routine blood banking or by a continuous centrifugation process known as platelet apheresis. A platelet transfusion should contain approximately 3-4 X 10^{11} platelets. This can be achieved with either 4 or more units of pooled single donor platelets (4 or more donor exposures) or a single platelet apheresis pack. Such an infusion in an adult 70 kg persons should raise the platelet count by 30-60,000/cc. These platelets infused have undergone a storage change/defect. Such defects include a shape change from discoid to spherical and the expression of many of the glycoprotein receptor sites used for signal transduction (GPIb, IIb/IIa etc). Platelets are stored at room temperature with gas permeable plastic materials. But, even with this and modern storage medias the platelet concentrates become progressively more acidotic and the cells clearly undergone metabolic stress. After 5 days of storage 40-60% of the platelets in the bags are essentially dead (ghosts) and many have budded platelet micro-vesicles. These platelet micro-vesicles are particularly pro-thrombotic particles or cell fragments. If one
transfuses platelets within 24-48 hours of harvesting and good collection storage practices are met then near 100% of the infused platelets may function normally. Whereas, if one infuses 7 day old platelets or ones that have been off of the shaker/agitator machine for some period there may be few if any platelets able to recover and function normally. Some work has suggested that in transportation of platelets (between blood bank centers) many units may be off the shaker machine for up to 24 hours. Work in platelet preservation has also shown the importance of pH, oxygen delivery and other inflammatory mediators such as compliment etc. Low pH particularly heralds adverse effects in platelets. Not only is low pH potentially a signal for potential bacterial contamination but it could well mean that the platelets in the bag have not been adequately moved and agitated during storage (allowing for permeation of oxygen). The low pH increases cell swelling and the expression of CD62 a cellular adhesion protein wherein platelets adhere to macrophages and other white cell mediators of inflammation. Of course when you and I infuse platelets, sent from the blood bank they are at a minimum 3 days old (due to HIV testing). We certainly know nothing of the pH in the bag and never reject them because they are “old” (5 days old). So when we transfuse platelets we assume they will function but in reality the percent of normally functioning cells is unknown (usually less than 50%). Those that do work tend to be hyper-reactive or pro-thrombotic. Once infused some cells do resume normal shape and function, but with a 10 day normal life span and at 4-5 day storage, at best some 40-50% of the cells will already be apoptotic or dead. As platelets die they do give off their cellular contents which are highly pro-thrombotic.

Platelet concentrates have previously had the highest risk of bacterial contamination. Today there is surrogate testing for such bacterial contamination yet sepsis is still probably at highest risk with platelet concentrates. What are the risks of low dose (not fully septic) units, that is hard to say? We simply do not know. Much of the prior work in platelet storage lesions and in bacterial contamination was carried out during the period when leukoreduced platelet concentrates were quite uncommon. Today, probably most platelet concentrates are leukoreduced from the time of collection though in the United States this is still quite variable. Certainly in Canada and in Western Europe leukoreduction universally occurs at the time of collection of the units. Does that somehow improve platelet storage defects? A debate still rages regarding this effect. But, in non-leukoreduced platelet concentrates the platelet leukocyte conjugates are very high. A problem we see in cardiopulmonary bypass heralded as a hallmark of inflammation of heart surgery.

Platelet concentrates are most widely utilized in bone marrow transplantation and treatment of leukemia etc. There exists a wide and growing literature showing an association between red cell transfusion and immune suppression in surgical patients. Still some argue about cause and effect but the literature, even from in vitro experiments shows that donor plasma has the ability to down-regulate opsonizing function of recipient white cells. In surgery we rarely, if ever, utilize ABO matched platelets in transfusion. In the treatment of acute myeloid leukemia and stem cell transplants the use of ABO-mismatched platelet transfusions is associated with an increased incidence of multi-system-organ failure and death. Allo-immunization is greatest with platelet
transfusions. If one is undertaking a program where-in heart transplantation will be a major part of the program or even repeat operations then subsequent cross-matching and matching for transplantation will be more difficult to impossible if widespread platelet transfusions are utilized. In matched platelet transfusions it has been shown that the in-vivo survival of platelets is longer when patients are matched to donor platelets. This was further seen in the leukemia patients in that the need for platelet transfusions was reduced 20-30% if ABO groups were matched. Further work from medicine patients, cancer patients, has noted a relationship between both RBC and platelet transfusions and adverse outcomes. In 504,208 cancer patients entered into the University Health System Consortium database between 1995-2003 from 60 US hospitals with a diagnosis of solid organ cancer, 11.7% received at least one RBC transfusion and 3% at least one platelet transfusion. Autologous transfusions had a very low rate of arterial (0.6%)and venous thromboembolism (0.9%). Whereas allogeneic transfusions were highly associated with arterial and venous thrombosis (OR 1.4 -95% CI 1.3-1.5). Death was highly associated with both RBC transfusion (OR 1.3- CI 1.3-1.4) and platelet infusion (OR 2.4- 95% CI 2.3-2.5).  

Platelet transfusions are highly associated with the risk for TRALI (Transfusion Associated Acute Lung Injury) and post transfusion fever. Clearly these two events are immune mediate. The mechanism for fever is thought to be that platelet transfusions carry a high level of CD40L which in the recipient triggers the release of PGE2 and IL-6. These then lead to fever whereas II-12 and other cytokines may well lead to further immune modulation. The levels of cytokines found in platelet concentrates (non-white cell reduced) have been noted to exceed 1000 times the levels found in healthy normal volunteers. These levels should be put in perspective as the levels of cytokines found in patients after cardiopulmonary bypass are 15-30 fold increased (not 1000 fold increased). TRALI is the #1 cause of mortality after blood transfusion. It is highly associated with the use of fresh frozen plasma and particularly platelet concentrates. Levels of potential immune mediator of TRALI are the highest in platelet concentrates.

Several papers exist regarding the risks of transfusion and outcome with respect to platelet transfusions. Yet a debate is present regarding whether platelet transfusions in heart surgery represent a risk for adverse outcome. There is no doubt that platelet transfusions in the face of severe coagulopathic bleeding represent a smaller risk, often, than that posed by the post-operative bleeding itself. In a retrospective data-based study of the Epi-II data Mangano and McSPI found that aspirin utilization after CABG surgery was related to improved outcome. However the following was also found: “The practices of discontinuing aspirin before surgery and transfusing platelets after reperfusion, as well as the prophylactic use of anti-fibrinolytic agents to reduce blood loss during the perioperative period, were associated with increased risks of death and ischemic complications”. These findings were striking and focused upon in table 3 of the paper. In the BART study as well as in the aprotinin papers since published from Epi-II the potential interaction between platelet transfusions and any one of or all the anti-fibrinolytic agents has not been examined with a detailed scientific analysis. Perhaps there exists an interaction that we do need to know about?
In 2004 we published a retrospective analysis of data from the combined aprotinin databases from all clinical trials of aprotinin for FDA approval from the Bayer database. These data had excellent data prospectively collected with regards to transfusion utilization and certain outcomes. They were from 6 randomized trials in some 37 (34 US, 1 Denmark and 1 Israel) institutions between 1990 and 1995. 1720 patients were analyzed from the database and 284 (14%) received one or more units of platelets. Interestingly only full dose aprotinin or placebo patients were analyzed. Half dose and pump prime aprotinin patients were excluded. These studies had no comparison with other anti-fibrinolytic agents at all. All units of blood utilized at this time were non-leukoreduced. Univariate, multivariate and propensity scoring analysis was performed with the data. Patients who received platelet transfusions were more likely to be older, non-Caucasian, have a low EF and have had a prior MI. So this was a high risk (for adverse outcomes) group that received platelet transfusions. Aspirin was around but at this time aspirin was routinely Dc’d prior to surgery and plavix had not appeared yet. 88% of patients who received platelet transfusions also received RBC transfusions. Those with more RBC transfusions received more platelet transfusions. Stroke (univariate analysis) was 0 units -1.3%, 1 unit- 7.5%, 2-3 units 10.5%). Correlations appeared between the use of platelet transfusions and the use of 2 or more inotropes, postoperative infection, respiratory complications and death. In multivariate analysis and propensity scoring analysis death stroke and vasopressor utilization remained as statistically significant when other potential risks were loaded into the models. Once again this study did not look at the interaction of aprotinin and platelet transfusion except to say that less were transfused in patients who received aprotinin.

Two other recent papers appear to contradict these findings from an earlier time. Karkouti K et al. examined 11,459 patients form their single institution undergoing heart surgery from 1999-2004. They did find a univariate effect and relationship between platelet transfusion and adverse outcome. These conclusions did not hold up once logistic regression and propensity score-case control analysis was applied. Also McGrath, Koch C et al. at a single center examined 32,298 patients for isolated CABG surgery with and without platelet transfusion. They, like Karkouti, concluded that univariate analysis did show a relationship between adverse events and platelet transfusions but with multivariate and propensity analysis these effects disappeared. So, where are we today? Are platelet transfusions safe, without effect upon outcome? The mechanistic work and data from earlier studies would suggest that platelet transfusions carry considerable risk. Is it that the two single centered studies represent “best practice” in terms of using platelet transfusions only for those who are actively bleeding? Or, are there effects of changing practice such as using leuko-reduced platelet concentrates that might be affecting these data? Ultimately, can we/should we design a prospectively randomized study with regards to platelet transfusions and heart surgery? What should be in the next iteration of the “Guidelines” for transfusion?

References


