REVIEW ARTICLE

Platelet Transfusion Therapy

*S Karim[1], E Hoque[2], MM Hoque[3], MMR Siddiqui[4]

[1]*Dr. Shanaz Karim, Assistent Professor of Transfusion Medicine, Dhaka Medical College Hospital*
[2]*Dr. Ehteshamul Hoque, Professor & Head of Oncology, AKMMCH*
[3]*Dr. Mazharul Hoque, Professor of Transfusion Medicine, Dhaka Medical College Hospital*
[4]*Dr. Md. Mahmudur Rahman Siddiqui, Assistant Professor of Medicine, AKMMCH*

*Corresponding Author

Date of submission: 11 March 2015 *Date of acceptance: 26 April 2015*

ABSTRACT

Patients with severe thrombocytopenia are presumed to be at increased risk for bleeding, and consequently it has been standard practice for the past four decades to give allogeneic platelet transfusions to severely thrombocytopenic patients as supportive care. Platelet transfusions may be given either prophylactically to reduce the risk of bleeding, in the absence of clinical hemorrhage (prophylactic transfusions), or to control active bleeding when present (therapeutic transfusions). Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood, which are pooled before administration, or by apheresis from single donors. Comparative studies have shown that the post transfusion increments, hemostatic benefit, and side effects are similar with either product. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are preferred when histocompatible platelet transfusions are needed. Both preparations can be stored for up to 5 days after collection at 20°C to 24°C with good maintenance of platelet viability. It is now uncommon for patients undergoing intensive chemotherapy or bone marrow transplantation to die of hemorrhage, but it is open to debate as to what degree platelet transfusions have been responsible for this change in outcome, given the many other advances in other aspects of supportive care.

Key Words: Thrombocytopenia, Platelets transfusion, Bleeding, Platelet concentrates (PCs.)

Introduction

Allogeneic platelet transfusions play a major role in the management of thrombocytopenic patients. The ready availability of platelet concentrates has made a major contribution to support the development of intensive treatment regimens for the treatment of patients with hematological and other malignancies. Although considerable advances have been made in many aspects of platelet transfusions in the last 30 years, several areas of controversy continue to exist with regard to the optimal approach to the use of platelet transfusions to further reduce the risk of clinically significant thrombocytopenic hemorrhage in patients with a hypoproliferative bone marrow and to minimize the frequency and severity of adverse events Platelets for transfusion can be prepared by three different methods: (a) the platelet-rich plasma (PRP) method; (b) the buffy coat (BC) method; and (c) the apheresis method[1,2] The PRP method, which is used almost exclusively in the United States, and the BC method, which is used predominantly in Western Europe and Canada, derive platelets from units of whole blood collected from volunteer whole blood donors.[2] Studies comparing PRP and BC platelets have shown no difference in the in vitro quality of such platelet concentrates when they are stored for up to 5 days; however, few studies of direct in vivo head-to-head comparisons of these two methods of preparing platelet concentrates have been done.[3] The third method for preparing platelets is by the process of apheresis.[4] One of the major advantages of using apheresis platelets is that enough apheresis platelets can be derived from a single donor to provide a single clinically relevant platelet transfusion dose to an adult thrombocytopenic patient. In contrast, to obtain the equivalent number of transfused platelets required using either the PRP or BC methodology requires the pooling of platelet concentrates from 4 to 6 different donors.

Prophylactic Platelet Transfusions

A number of Clinical Practice Guidelines have been published in both Europe and North America that provide "evidence-based" recommendations for the clinical use of platelet transfusions. In general, they recommend prophylactic platelet transfusions at a transfusion trigger of 10×10^9/ L[4,5,6,7] The use of therapeutic platelets is only recommended when there is significant bleeding or when an invasive intervention is anticipated.

It was not until the early 1970s that platelet transfusions became part of standard treatment in the management of thrombocytopenic patients with a hypoproliferative bone marrow.[8] At that time, several observational studies were conducted to determine the possible role of prophylactic platelet transfusions to reduce the risk of clinical bleeding. Based on such studies, it became common practice to transfuse platelets prophylactically to patients with platelet counts below 20×10^9/L. It is important to note, however, that this practice was largely based on data from non-randomized studies, which indicated that bleeding was mainly evident in patients who had platelet counts of less than 5 × 109/L compared to patients with platelet counts between 5 and 100×10^9/L.[9], Thus, even though the incidence of bleeding across the range between 5 and 100×10^9/L showed little difference, the threshold of 20×10^9/L was widely adopted. Only in the late 1990s and early part of the twenty-first century were various studies done to try to establish an optimal prophylactic platelet count threshold for prophylactic platelet transfusions in thrombocytopenic patients.[8,10,11,12,13] The most widely quoted trial, which used a lower prophylactic trigger of 10×10^9/L versus 20×10^9/L, was evaluated in a multicenter, randomized clinical trial (RCT).[10] This group studied adult patients receiving induction therapy for newly diagnosed AML. The primary objective of this two-arm RCT was to determine the frequency and severity of hemorrhage in patients receiving prophylactic platelet transfusions. The two arms in the trial were the control arm in which the subjects were given platelets if the morning platelet count was less than 20×10^9/L or if bleeding; and the experimental arm, which included subjects who received platelet transfusions when their morning platelet counts were less than 10×10^9/L. Higher doses of platelets were given if study subjects were found to be actively bleeding or had a temperature higher than 38°C. The results of this trial provided data that there was no significant difference between the two arms in severe bleeding events or mortality.

Since then there have been at least 7 other studies that have evaluated the optimal threshold level for triggering prophylactic platelet transfusions at platelet counts of 10×10^9/L versus the previously accepted trigger of 20×10^9/ L (reviewed in Slichter[8]). Overall, 4 of these studies were RCTs (including the one by Rebulla et al10) and 3 were non-randomized. Uniformly, these 7 studies showed no increase in bleeding risk or the need for more RBC transfusions when the lower transfusion trigger was used. Although 3 of the studies showed a substantial decrease in the number of platelet transfusions required in the subjects who received platelet transfusions based on the lower platelet transfusion trigger (10×10^9/L), but it is of note that 4 studies did not. Interestingly, none of the 7 studies showed evidence of a difference in clinical outcomes in either arm, and this is a general theme across all clinical trials of platelet transfusion. It is also debatable whether these trials were adequately powered to demonstrate equivalence in outcomes.[6]

Based on such studies as well as several additional observational studies, there has been increasing interest in determining whether an even lower platelet transfusion trigger (5×10^9/L) could provide effective hemostasis in thrombocytopenic subjects.[8,9] The more recent studies provided evidence that it might be possible to reduce the prophylactic platelet transfusion trigger even lower than the currently accepted standard of 10×10^9/L[9] although several recent studies have highlighted the inaccuracies of hematology analyzers in platelet counting in patients with severe thrombocytopenia.[14,15]

Therapeutic Platelet Transfusions

As indicated above, standard practice in most hemato-oncology units in the developed world has been to use prophylactic transfusions, and to use therapeutic transfusions only when significant clinical bleeding occurs or before an invasive intervention is undertaken. A relatively recent publication has again raised the issue about the use of therapeutic transfusions only versus the widely used threshold-defined prophylactic platelet transfusions approach[16] In a retrospective review of almost 3000 thrombocytopenic adult patients over a 10-year period Friedman et al, by using multiple

logistic regression analysis, showed no relationship between the first morning platelet count, or the lowest platelet count of the day, and the risk of hemorrhage.[16] This study identified several important patient-specific factors that appear to be associated with a greater risk for severe bleeding. These include a history of recent bleeding, uremia, a recent (less than 100 days) bone marrow transplant, and hypoalbuminemia[16].

Further support for the absence of a relationship between the severity of thrombocytopenia and hemorrhage came from a review of case reports of severe intracranial hemorrhage described in trials of prophylactic platelet transfusions where no clear evidence could be found for an association between the occurrence of major intracranial bleeding and absolute platelet count just prior to the onset of severe hemorrhage.[17]

Thus, the overall benefit of a prophylactic platelet transfusion policy over a policy to use platelets only therapeutically is not well established. It is important to note that there are now some data, albeit observational, to suggest that a treatment-based platelet transfusion strategy may indeed be safe and effective in clinical practice. This is exemplified by the results of a recent study of therapeutic platelet transfusions in hematopoietic stem cell autograft patients in Germany.[17] It is also possible that patient selection may be the key to the safety of therapeutic only-based platelet transfusion.

PCs from Whole Blood. Often referred to as random-donor platelets, PCs are prepared by centrifugation of standard units of whole blood. There are two methods for doing this: (1) the platelet-rich plasma (PRP) method, and 2) the buffy coat (BC) method.18 The PRP method is used in the United States, whereas the BC method is in common use in Europe. In the PRP method, an initial low G force (soft) spin produces PRP, which is separated from the red cells. The PRP is then centrifuged at a higher G force (hard) spin, and most of the platelet-poor plasma is removed[19,20,21,22] The residual PCs contain approximately 0.5 to 0.75×10^{11} platelets/unit or approximately 60% to 75% of the platelets from the original unit of whole blood. Because some blood centers now supply units with higher numbers of platelets, clinicians should be aware of the average dose provided by their particular center. One drawback to this method is that the resulting PCs also contain 10^8 to10^9 WBCs or approximately 50% or more of the leukocytes from the original unit of whole blood.

This combination of storage container, agitation, preservative solution, temperature, and the use of approximately 50 mL of plasma permits satisfactory preservation of platelets for up to 7 days[23,24] However, several instances of bacterial contamination of PCs stored for this period have been reported[25,26] and the storage time from collection to transfusion is is now limited to 5 days.[27] Because several units of PC are pooled to obtain a dose for one transfusion, one reason to use single-donor apheresis platelets is to minimize the number of donors to which the patient is exposed and, theoretically, to minimize the likelihood of disease transmission. Although this may be a relevant consideration in patients who receive only a few transfusions in total, there is no evidence, particularly with contemporary screening and testing techniques, that there is any difference in the incidence of transfusion-transmitted infections in oncology patients who often require dozens of donor exposures to RBC and platelet donors during their lifetime.

When histocompatible platelets are required for patients refractory to random donor transfusions, platelets for subsequent transfusions should be from selected donors and, thus, single-donor platelets are the only platelet product that is available for these transfusions. Most patients require a dose of platelets larger than can be provided by platelets from one unit of whole blood, and several PCs are usually pooled to obtain an appropriate dose for most patients. If the volume of plasma in the final pooled component is too large, as might be the case for some pediatric recipients, some of the plasma can be removed before transfusion. From 15% to 55% of platelets are lost during this additional centrifugation step28,29 Volume reduction should therefore be limited to patients who require severe volume restriction or situations where ABO incompatible platelets are the only available PC for a neonate or child.

Single-Donor Platelets Produced by Apheresis. Although the Food and Drug Administration term for this component is "platelets, apheresis," the component is usually called single-donor platelets. Donors usually undergo two venipunctures. Blood pumped from one vein passes through a blood-cell separator centrifugation system with removal of the

platelets or other cellular components and return of the plasma and RBCs to the donor's other arm. Plateletpheresis usually requires approximately11/2 to 2 hours and involves processing 4,000 to 5,000 mL of the donor's blood.[30,31,32,33,34,35,36] This results in a plateletpheresis product that contains the number of platelets equivalent to six to nine units of PC prepared from whole blood. However, many centers have recently begun to split their apheresis collections into two products so that the dose may actually be more equivalent to four to five units of PC. Clinicians are therefore advised to check on the policies of their local blood supplier so as to best determine the appropriate number of units or apheresis products to transfuse in particular clinical situations. Current standards require that a bag of apheresis platelets must contain at least 3×10^{11} platelets in at least 75% of the products tested.[37]

Platelets obtained by plateletpheresis are processed, tested, and labeled similar to whole blood. This includes ABO and Rh typing and testing for all required transfusion-transmitted diseases. The plateletpheresis product is stored for up to 5 days at 20°C to 24°C.[30,38,39,40,41] in the same manner as platelets prepared from whole blood. The number of platelets contained in each bag is determined, although this information may not be recorded on the label. Each apheresis product has a volume of approximately 200 mL and contains few red cells, so that red cell crossmatching is not necessary. The WBC content varies, depending on the instrument and technique used for collection, but most plateletpheresis products now contain less than 5×10^{6} leukocytes and can be considered to be leukocyte reduced (see below).

Clinical Use of Random Donor Whole-Blood or Single-Donor Platelets. The mix of random-donor whole-blood and single-donor apheresis platelets provided to different medical centers varies considerably, depending on local philosophy, patient mix, blood supply availability, cost, and transfusion-transmitted disease risk. Because several units of PC are pooled to obtain a dose for one transfusion, one reason to use single-donor apheresis platelets is to minimize the number of donors to which the patient is exposed and, theoretically, to minimize the likelihood of disease transmission. Although this may be a relevant consideration in patients who receive only a few transfusions in total, there is no evidence, particularly with contemporary screening and testing techniques, that there is any difference in the incidence of transfusion-transmitted infections in oncology patients who often require dozens of donor exposures to RBC and platelet donors during their lifetime. When histocompatible platelets are required for patients refractory to random donor transfusions, platelets for subsequent transfusions should be from selected donors and, thus, single-donor platelets are the only platelet product that is available for these transfusions.

Discussion

In 1982, Murphy et al[42] published a prospective randomized trial comparing prophylactic and therapeutic transfusion policies in 56 pediatric leukemia patients treated from 1972 to 1976. The prophylactic threshold was set at 20,000 platelets/μL. Although patient survival was not significantly different in the two groups, the prophylactic policy was associated with a significant reduction in the number of days with hemorrhage. However, patients in the prophylactic arm suffered from more prolonged hemorrhagic episod possibly as a result of the development of HLA alloimmunization and refractoriness to random-donor platelet support. Other data supporting a prophylactic policy were published by Gaydos et al[43] and by Slichter and Harker.[44] In a study dating from the early 1960s, Gaydos et al showed that hemorrhage was more frequent and severe at platelet counts below 5,000/μL, whereas it occurred in 8% and 4% of hospital days at counts exceeding 10,000/μL and 20,000/μL, respectively. Other data supporting a prophylactic policy were published by Gaydos et al[43] and by Slichter and Harker.[44] In a study dating from the early 1960s, Gaydos et al showed that hemorrhage was more frequent and severe at platelet counts below 5,000/μL, whereas it occurred in 8% and 4% of hospital days at counts exceeding 10,000/μL and 20,000/μL, respectively. These observations were made in an era when aspirin was frequently used as an antipyretic and when antibiotic coverage for Gram-negative organisms was inadequate by contemporary standards. Of note, these authors could not identify a threshold at which the rate of bleeding increased, and they emphasized the importance of other factors predisposing to bleeding. Slichter and Harker found that daily blood losses in stools from patients with aplastic anemia were 9 ± 7 mL at platelet counts of

5,000/μL to 10,000/μL but increased to 50±20 mL at counts below 5,000/μL.

Thus, although there are no contemporary randomized studies comparing the incidence of serious bleeding and patient survival in patients receiving prophylactic versus therapeutic platelet transfusions, the prophylactic approach has become standard practice.[45,46,47] Fatal hemorrhage is now an unusual event, even in patients with bone marrow failure or in those receiving intensive antineoplastic therapy. However, it should be emphasized that not all thrombocytopenic patients require or benefit from platelet transfusion and that the decision to administer transfusion is not based solely on the platelet count but should be individualized for specific clinical settings, as discussed below. Platelet transfusion is generally reserved for patients with impaired marrow production of platelets, is rarely needed in patients with increased platelet destruction such as autoimmune or drug-associated immune thrombocytopenia, and is relatively contraindicated in patients with thrombotic thrombocytopenic purpura because of concerns about the risk of precipitating thromboses.[46,47] Gmür and Schaffner[48] reported that their protocol could also be applied using random-donor platelets rather than single-donor, apheresis platelets.

The most recently published evidence supporting the safety of the 10,000/μL threshold was reported in 1998 by Wandt et al[49] who studied 105 leukemia patients undergoing 216 remission-induction or consolidation treatment cycles in 17 centers in Germany. Individual participating centers had prevhad previously chosen to adopt either a 20,000/μL or a 10,000/μL threshold level for their prophylactic transfusion policy. In this study, there were 20 bleeding complications (18%) in 110 chemotherapy cycles in the 10,000/μL group and 18 (17%) in 106 cycles in the 20,000/μL group. Hemorrhagic deaths occurred in two patients at platelet counts of 36,000/μL and 50,000/μL treated in hospitals using the 20,000/μL threshold. Mean platelet consumption per cycle was one third lower in the 10,000/μL group.

It should be reiterated that all of these studies had provisions for transfusion at counts greater than 10,000/μL in patients with clinical conditions believed to be associated with increased risks of bleeding. In addition, although contemporary blood cell counters are quite accurate at low platelet counts, small variations in count can result from limitations of the technology, and the decision to transfuse should therefore be based on the clinical situation and the pattern of recent platelet counts as well as the absolute platelet count at a given moment.[50]

Conclusion

Fatal hemorrhage is now an unusual event, even in patients with bone marrow failure or in those receiving intensive antineoplastic therapy. However, it should be emphasized that not all thrombocytopenic patients require or benefit from platelet transfusion and that the decision to administer transfusion is not based solely on the platelet count but should be individualized for specific clinical settings.. Platelet transfusion is generally reserved for patients with impaired marrow production of platelets, is rarely needed in patients with increased platelet destruction such as autoimmune or drug-associated immune thrombocytopenia.

Patients with severe thrombocytopenia are clearly at an increased risk for bleeding, and the standard approach for treating such patients is the use of allogeneic platelets, particularly in those with a hypoproliferative marrow function (i.e., those with thrombocytopenia following chemotherapy). Thus, platelet transfusions can be given either prophylactically to reduce the risk of bleeding or to control bleeding when bleeding is actually occurring (therapeutic transfusions); however, the approach to the optimal use of platelet transfusions to reduce the risk of clinically significant bleeding in such patients is unclear. The place of therapeutic platelet transfusions and whether prophylactic are superior to therapeutic platelet transfusions for the prevention and control of thrombocytopenic bleeding is thus a question that remains unanswered

Conflict of Interest

The authors have no conflict of interest to anybody.

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