Platelet transfusion therapy

Balen, Sanja

UDK 615.381
Review article
Received: 28 May 2015
Accepted: 16 September 2015

PLATELET TRANSFUSION THERAPY

Sanja Balen[a,b]

[a]Clinical Institute for Transfusion Medicine, Clinical Hospital Center Rijeka;
Department for Clinical Laboratory Diagnostics;
[b]Medical Faculty, University of Rijeka, Rijeka, Croatia

Summary

Since the 1960s, platelet transfusion therapy has played a vital role in the management of hematologic and oncologic patients with quite frequent disorder: thrombocytopenia. More than 2.9 million platelet components are transfused each year in Europe and 57,000 in Croatia. Indeed, platelet transfusion has long been the subject of many debates and controversies, including the advantage of giving prophylactic compared to therapeutic transfusion, the trigger and/or threshold for platelet transfusion, the platelet collection method, and the optimal platelet dose to be transfused. Taking into account a short shelf life of PLTs compared to other blood components (5 to 7 days) and a growing demand for their use, each transfusion center must decide on its own priorities for providing a sufficient quantity of safe and effective PLT units.

Keywords: Platelets, prophylactic, therapeutic transfusion, transfusion trigger

INTRODUCTION

Since the 1960s, platelet transfusion therapy has played a vital role in the management of hematologic and oncologic patients with thrombocytopenia [1]. Although platelets are essential in the maintenance of normal hemostatic activity, for patients with thrombocytopenia (low platelet counts) or impaired platelet function, platelet transfusion can be of significant value in preventing and treating hemorrhage [1,2]. Nowadays, many modern therapies depend on platelet transfusion support. There is an increasing demand for platelet transfusions due to intensive chemotherapy and blood stem cell or bone marrow transplantation, but also as support in numerous medical treatments in general, such as major surgery, trauma resuscitation, and various diagnostic procedures in thrombocytopenic patients. More than 2.9 million platelets are transfused in Europe each year and 57,000 in Croatia [3]. However, the supply of platelets is limited worldwide and platelet transfusion is considered a financially burdensome and challenging procedure.

In the majority of cases (more than 70%), platelet transfusions are used prophylactically, to prevent spontaneous bleeding by maintaining the platelet count above a predetermined transfusion trigger. In a bleeding patient with thrombocytopenia, platelets are transfused therapeutically, in order to achieve hemostasis [2,4-6]. There are still debates and controversy regarding the trigger for platelet transfusion, the optimal platelet dose to be transfused and the advantage of giving prophylactic compared to therapeutic transfusion. The decision to administer platelet transfusions should incorporate individual clinical characteristics of the patient and not simply be a reaction to the platelet count.

Manufacture of platelet units

Platelets (PLTs) for transfusion can be collected by apheresis technology (Figure 1.) or prepared from whole blood. In the latter case, whether PLT unit is prepared from the buffy coat or from platelet-rich plasma, four to six donor units are pooled together to produce an adult dose of PLTs. The number of PLTs per random donor pool varies according to the PLT count of each single donor; a yield of 3-4 x 10^{11} is preferred. Advantages of pooled platelets, when compared to apheresis, are lower cost and ease of collection and processing. The major disadvantage is recipient exposure to multiple donors in a single transfusion [7].

A typical apheresis platelet unit (single donor platelets) provides the equivalent of six or more units of PLTs from whole blood (i.e. 3 to 6 x 10^{11} PLTs). Advantages of apheresis platelet unit are recipient exposure to a single donor and the ability to match donor and recipient human leukocyte antigens (HLA) type, human platelet antigens (HPA) type and ABO blood type for certain recipients [2,7,8].

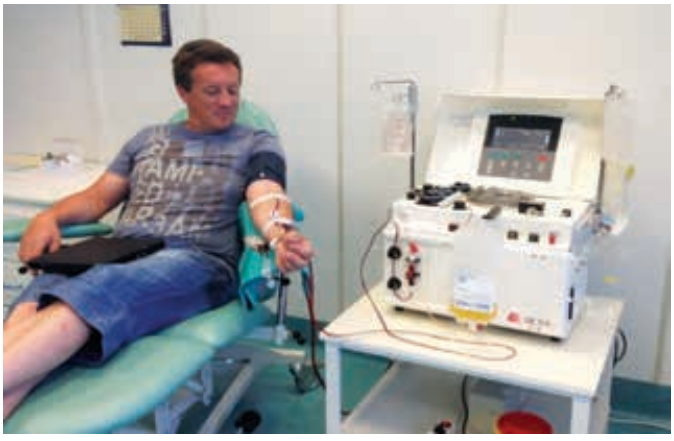

Figure 1. Donor Plateletpheresis

Standard therapeutic dose of PLTs refers to 1 apheresis platelet unit or a pool of 4 to 6 whole blood–derived platelet concentrates, containing 3 to 4 × 10^{11} PLTs. Platelets are collected in bags that allow oxygen and carbon dioxide gas exchange, and stored at room temperature in special conditions (Platelet incubator with agitator - Figure 2.). The shelf life of stored platelets is five days (4-7) and they are frequently in short supply [2,7,9].

Figure 2. Platelet incubator with agitator

MODIFICATIONS OF PLATELET UNITS

Each unit of whole blood or unmodified platelet unit contains 2 to 5 x 10^9 contaminating leukocytes. Platelets can be leukoreduced to help prevent some transfusion reactions, such as febrile non-hemolytic reactions, HLA alloimmunization, transmission of different viruses (CMV, HTLV ½, EBV, HTLV, HSV, etc.), transfusion related acute lung injury (TRALI), and reduction of transfusion-associated immunomodulation [7]. There are two major categories of leukoreduced platelets: prestorage and poststorage. The most effective current leukocyte reduction filters generally leave residual leukocyte counts below 1 x 10^6.

Platelets can also be irradiated with a minimum dose of gamma irradiation of 25 Gy in some clinical conditions, such as immunocompromised patients, bone marrow or stem cell transplants, intrauterine transfusions, neonatal exchange transfusion,

relative blood donors, and genetically homogeneous populations or HLA matched platelets. Irradiation inhibits the proliferation of viable T lymphocytes preventing serious side effect of transfusion therapy – transfusion associated graft versus host disease (ta-GvHD) [7].

Washed platelets are rarely prepared, only in the case of severe allergic or anaphylactic reaction to plasma proteins or in patients with existing anti-IgA antibodies due to IgA deficiency [10].

Volume-reduced platelets should be used in case of ABO-minor mismatched platelets or for transfusion of volume-sensitive patients [11].

Dosage and refractoriness to platelet transfusion

It is considered that the optimal dose of platelet transfusion for children is 0.5×10^{11}/10 kg, which is equivalent to one whole blood-derived platelet concentrate and 3.0×10^{11} in adults, which is one apheresis unit or a pool of 4-5 random donor platelets. Each platelet unit from whole blood should increase the platelet count by 5-10,000 x 10^9/L in an average non-bleeding adult. This is roughly equivalent to a rise of 30,000/μL in platelet count in an average adult patient transfused with one unit of single donor apheresis platelets or an equivalent pool of random donor platelet. The 10-minute and 1-hour post-transfusion platelet count increment can provide useful data on patient response to platelet transfusion. It is usually defined as platelet recovery**.** The formula most commonly used to calculate platelet count increment is:

Absolute PLT increment/μL x body surface area (m^2) / Number of transfused PLTs (10^{11})

The expected corrected platelet increment (CCI) after 10 minutes should be greater than 10,000/μL per m^2 of body surface area. Platelet increments less than 5,000/μL indicate refractoriness. Platelet survival is evaluated by a platelet count obtained 24 hours post-transfusion. It is considered that the platelet survival is satisfactory if the CCI is greater than 4,500/μL. Refractoriness to platelet transfusion may be caused by immune and non-immune mechanisms. Normal platelet recovery means normal increment at one hour following transfusion, with return to the baseline count within 24 hours (reduced platelet survival), and is typical for non-alloimmune causes. It is considered that a large number of refractory episodes occur because of non-immune causes, such as sepsis, high fever, bleeding, splenomegaly, disseminated intravascular coagulation (DIC) and medications. In cases of non-immunological mechanism, it is necessary to treat the underlying cause of the disease, and increase the dosage of platelet units at least three times [7,12].

Refractoriness related to alloimmunization is caused by the antigens on the platelet surface, such as HLA Class I, HPA and ABO antigens. Reduced platelet re-

covery (little or no increment in platelet count) within one hour of transfusion, demonstrated after at least two transfusions, is caused by alloimmunization. In cases of immune-mediated refractoriness, there are several strategies to consider when selecting platelets for such patients: provision of HLA-matched platelets or HLA "compatible" (antigen-negative) platelets, platelets selected by crossmatch tests (crossmatch-compatible platelets), and other medical treatments to reduce alloimmunization. Some cases of refractoriness are a combination of both immune and non-immune mechanisms [7,13,14].

There has been a long-lasting debate over whether the traditional threshold for prophylactic platelet transfusion of 20,000/μl is really necessary to prevent hemorrhagic complications. During the last 10 years several studies have proven the safety of more restrictive platelet transfusion strategies with a platelet transfusion trigger of 10,000/μl or even lower when patients are clinically stable without active bleeding. Such a strategy decreases the risk of infectious disease transmission, early immunization, febrile and allergic transfusion reactions, and other discomforts for the patient, such as frequent hospital visits or a longer hospital stay, and reduces the costs of platelet transfusions by 20% - 30% compared with traditional transfusion strategies [2,4,15-17]. There are some widely accepted recommendations for prophylactic platelet transfusions in various clinical settings (Table 1.) [12].

Table1. Recommendations for prophylactic platelet transfusions

Transfusion trigger No. of platelets x 10^9 /L	**Recommendations for platelet transfusions**
$<10 \times 10^9$ /L	Prophylactically, to prevent spontaneous bleeding (afebrile patients)
$<20 \times 10^9$ /L	Preparing for bone marrow aspiration/biopsy or elective central venous catheter placement, for low risk diagnostic procedures
$<30\times 10^9$ /L	Prophylactically, to prevent spontaneous bleeding in fever, infection or sepsis, splenomegaly
$<50 \times 10^9$ /L	Preparing for elective diagnostic lumbar puncture, endoscopic procedures or major elective surgery
$<100 \times 10^9$ /L	Preparing for intracranial (central nervous system) or intraocular bleeding; for neurosurgery or ocular surgery

There is no doubt that platelets should be transfused therapeutically, regardless of the PLTs number in actively bleeding patients with thrombocytopenia, massive blood loss, disseminated intravascular coagulation or cardiopulmonary bypass.

Platelet transfusions are not recommended in patients with immune thrombocytopenia, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) and heparin-induced thrombocytopenia (HIT), only if patients have serious bleeding, are at high risk of bleeding (e.g., after surgery), or require invasive procedures [12].

Platelet characteristics, such as platelet dose, platelet source (apheresis vs. pooled), platelet donor-recipient ABO compatibility, and duration of platelet storage, can affect post-transfusion platelet increments, but it is still unclear whether these factors impact platelet transfusion efficacy on clinical bleeding. Majority of clinical studies shows that they have no measurable impact on prevention of clinical bleeding [18].

Adverse effects of transfused platelets and their prevention

It is possible to decrease the incidence of alloimmunization to HLA Class I antigens and subsequent alloimmune platelet refractoriness by utilizing leukocyte-reduced platelet units for transfusion (leukoreduction to below 1×10^6 cells). Patients who are alloimmunized and refractory to platelets are often difficult to manage, so it is helpful to try to prevent alloimmunization by transfusing leukoreduced blood products in patients likely to require long transfusion support [7,19].

Platelets express ABH antigens on their surface. It is recommended to give a transfusion of ABO- compatible or identical platelets whenever possible. In many transfusion centers, platelets are transfused without regard to ABO compatibility, due to short supply. Transfusions of ABO-incompatible platelets are associated with a reduced post-transfusion increment due to minor or major ABO mismatched transfusions, although the clinical significance is minimal and/or unclear. In ABO-minor mismatched platelets there are anti-A or anti-B antibodies, or both, which are incompatible with the recipient's red blood cells, but there is a small risk of hemolytic reaction that could be avoided by reducing the volume of incompatible plasma in platelet units. In ABO-major mismatched platelets there are ABH antigens on the surface of the platelets that can be destroyed by the recipient's anti-A and/ or anti-B antibodies, resulting in decreased post-transfusion platelet increments [20,21,22].

Platelet units also contain a small number of red blood cells that express Rh antigens on their surface, which platelets do not express. The rate of anti-D alloimmunization following the D+ platelet transfusion to a D- recipient is very low and depends on a variety of the patient's clinical circumstances. However, transfusion centers avoid giving platelets from D^+ donors to D^- female patients because of the potential risk of RhD alloimmunization. In the case of transfusing D+ platelets to a D- recipient, Rh immune globulin (RhIg) should be administered to prevent D alloimmunization [20,23].

Despite significant improvements in donor screening and laboratory testing, a small risk of viral, bacterial and protozoal contamination of platelets still exists. Some viruses, such as CMV (EBV, HTLV1/2), are transmitted by contaminated leukocytes and could be avoided by leukoreduction. Bacterial contamination is more common in platelets than in red cell units due to storage at room temperature. The risk of bacterial infection could be reduced by appropriate skin sterilization techniques during collection and by discarding the first 15 to 30 mL of blood collected, using assays to screen for bacterial contamination or using some of the methods of pathogen reduction or inactivation [7,9].

One of the rare but serious complications of platelet transfusion is transfusion-associated graft-versus-host disease (ta-GvHD) that is mediated by viable donor lymphocytes. It occurs in two clinical settings: when the recipient is immunodeficient or immunosuppressed (e.g., from hematopoietic cell transplant and lymphoma), and when there is a specific type of partial HLA matching between the donor and the recipient. The treatment of choice to prevent ta-GVHD is irradiation of platelet units [7].

Platelet units also contain plasma which can be implicated in adverse reactions, including severe allergic anaphylactic reaction to plasma proteins and transfusion-related acute lung injury **(**TRALI**),** a form of acute lung injury that causes respiratory distress following transfusion. The risk of severe allergic and anaphylactic reaction could be reduced by using washed platelets. TRALI could be avoided by using platelets from male donors only, removing the plasma from the platelets and /or resuspending the platelets in platelet additive solutions [7].

Transfusion of platelets may be associated with circulatory overload: transfusion-associated circulatory overload (TACO). The incidence of TACO is higher in patients predisposed to volume overload (e.g., in the elderly, in small children weighing up to 15 kg and in patients with congestive heart failure, renal failure, respiratory failure and positive fluid balance) [7].

Post-transfusion purpura (PTP) is a rare transfusion reaction that occurs in less than 2 percent of individuals who lack human platelet antigen 1a (HPA-1a), and have developed anti- HPA-1a antibody. Thrombocytopenia develops 5 to 10 days following transfusion [7].

CONCLUSIONS

Many modern medical treatments and diagnostic procedures in thrombocytopenic patients depend on a constant supply of PLTs. The question still remains when platelets should be administered to minimize the risk of bleeding while maximizing their benefit. There are still no substitutes for platelet transfusion that could

rapidly increase the platelet count in a bleeding patient. Given the high demand for their use, compromises must be made between providing the "ideal" platelet unit and the realities of blood bank supply. Each transfusion center must decide on its own priorities for providing safe and effective PLT transfusions.

References

[1] Wandt H, Ehninger G, Gallmeier WM. New strategies for prophylactic platelet transfusion in patients with hematologic diseases. Oncologist 2001; 6(5):446-50.

[2] Blajchman MA, Slichter SJ, Heddle NM, Murphy MF. New strategies for the optimal use of platelet transfusions. Hematology Am Soc Hematol Educ Program. 2008:198-204. doi: 10.1182/asheducation-2008.1.198.

[3] Tomičić M, Vuk T, Hundrić-Hašpl Ž. Indikacije i kontraindikacije za primjenu trombocitnih transfuzija u bolesnika s trombocitopenijom. Liječnički vjesnik 2014; 136: 90-93.

[4] Kumar A, Mhaskar R, Grossman BJ, et al**.** Platelet transfusion: a systematic review of the clinical evidence. Transfusion. 2014 Nov 12. doi: 10.1111/trf.12943. [Epub ahead of print]

[5] McCullough J. Overview of platelet transfusion. Semin Hematol. 2010 Jul; 47(3):235-42.

[6] Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. 2010; 362(7):600–613.

[7] Grgičević D i sur. Transfuzijska medicina u kliničkoj praksi, Medicinska naklada 2006.

[8] Heddle NM, Arnold DM, Boye D, Webert KE, Resz I, Dumont LJ. Comparing the efficacy and safety of apheresis and whole blood-derived platelet transfusions: a systematic review. Transfusion. 2008; 48(7):1447–1458.

[9] Cochrane Database of Systematic Reviews: Platelet transfusions, treated to reduce transfusion-transmitted infections, for the prevention of bleeding in patients with low platelet counts. Review content assessed as up-to-date: February 25, 2013.

[10] Tynngard N, Trinks M, Berlin G. Platelet quality after washing: the effect of storage time before washing. Transfusion. 2010; 50:2745–2752.

[11] Veeraputhiran M, Ware J, Dent J, et al. A comparison of washed and volume-reduced platelets with respect to platelet activation, aggregation, and plasma protein removal. Transfusion. 2011; 51:1030–1036.

[12] Kaufman RM, Djulbegović B, et al. Platelet Transfusion: A Clinical Practice Guideline From the AABB**.** Ann Intern Med. 2015; 162(3):205-213. doi: 10.7326/M14-1589**.**

[13] Pavenski K, Rebulla P, Slichter SJ, et al. Efficacy of HLA-matched platelet transfusions for patients with hypoproliferative thrombocytopenia: a systematic review. Transfusion. 2013 Oct; 53(10):2230-42. doi: 10.1111/trf.12175. Epub 2013 Apr 3.

[14] Vassallo RR, Fung M, Rebulla P, et al. Utility of cross-matched platelet transfusions in patients with hypoproliferative thrombocytopenia: a systematic review. Transfusion. 2014 Apr; 54(4):1180-91. doi: 10.1111/trf.12395. Epub 2013 Aug 27.

[15] Benjamin RJ. The effect of various platelet dosing strategies on transfusion costs. Transfusion. 2012; 52:1852–4.

[16] Wandt H, Schaefer-Eckart K, Wendelin K, et al.Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet. 2012 Oct 13; 380(9850):1309-16.

[17] Tarek Bou Assi, Antoine Haddad, and Elizabeth Baz. Clinical effectiveness and comparative hospital costs of different platelet dose strategies. Blood Transfus. 2014 Jul; 12(3): 307–313.

[18] Triulzi DJ, Assmann SF, Strauss RG, et al. The impact of platelet transfusion characteristics on posttransfusion platelet increments and clinical bleeding in patients with hypoproliferative thrombocytopenia. Blood. 2012 Jun 7; 119(23):5553-62.

[19] Ratko TA, Cummings JP, Oberman HA, et al. Evidence-based recommendations for the use of WBC-reduced cellular blood components. Transfusion 2001; 41:1310.

[20] Cid j, Harm SK, Yazer MH. Platelet Transfusion – the Art and Science of Compromise. Transfus Med Hemother. 2013 Jun; 40(3):160-71.

[21] Shehata NS, Tinmouth A, Naglie G, Freedman J, Wilson K. ABO-identical versus nonidentical platelet transfusion: a systematic review. Transfusion. 2009; 49(11):2442–2453.

[22] Dunbar NM, Ornstein DL, Dumont LJ. ABO incompatible platelets: risks versus benefit. Curr Opin Hematol. 2012; 19:475–479.

[23] Bartley AN, Carpenter JB, Berg MP D+ platelet transfusions in D- patients: cause for concern? Immunohematology 2009; 25(1):5-8.

Sažetak

Transfuzijsko liječenje koncentratima trombocita

Od ranih 60-ih godina prošlog stoljeća, transfuzija koncentrata trombocita ima značajnu ulogu u liječenju hematoloških i onkoloških bolesnika s trombocitopenijom. Svake se godine u Europi transfundira više od 2,9 milijuna koncentrata trombocita i 57.000 u Hrvatskoj. Trombocitne transfuzije već su dugi niz godina predmet brojnih rasprava i kontroverzi, posebice prednost profilaktičke u odnosu na terapijske transfuzije, okidač / ili prag za transfuziju trombocita, metode prikupljanja trombocita te optimalnu dozu trombocita za transfuziju. Uzimajući u obzir da trombociti imaju kratak vijek trajanja u odnosu na druge krvne pripravke (5-7 dana), uz rastuće zahtjeve za njihovo korištenje, svaki transfuzijski centar mora odlučiti na koji će način osigurati dovoljan broj sigurnih i učinkovitih koncentrata trombocita.

Ključne riječi: trombociti, profilaktičke, terapijske transfuzije, transfuzijski prag

Corresponding author:
Sanja Balen
E-mail:sanja.balen@medri.uniri.hr