Platelet Transfusion Therapy

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KEYWORDS

• Platelet transfusion • Alloimmunization • Transfusion triggers • Pathogen reduction

KEY POINTS

- In the United States, platelets are collected in citrate anticoagulants from single units or by apheresis procedure.
- To prevent bleeding in thrombocytopenic patients, it is a common practice to transfuse platelets when platelet counts reach a trigger threshold (prophylactic transfusion).
- The transfusion of all blood products including platelets can cause viral infection, such as hepatitis B, C, West Nile virus, and HIV, although the modern nucleic acid–based testing has reduced the risk to a very low level.
- Platelet transfusions are considered risky in patients with thrombotic thrombocytopenic purpura because it can exacerbate the microvascular thrombosis.
- Because treatment of alloimmune refractory thrombocytopenia is difficult, costly, and often ineffective, it is critical to prevent alloimmunization.

HISTORICAL PERSPECTIVE

Duke reported the earliest platelet transfusion in a landmark article at the beginning of the last century in 3 patients with idiopathic thrombocytopenic purpura.[1] He achieved temporary cessation of bleeding and an increase in platelet count in 2 patients by transfusing directly the unmodified whole blood. These earlier attempts were limited by lack of platelet concentrates and in vitro activation of platelets. The modern era of platelet transfusion started with demonstration by Gaydos and colleagues[2] that prophylactic transfusions of platelets in patients receiving chemotherapy dramatically reduced the incidence of fatal bleeding complications and allowed completion of chemotherapy. They also pioneered apheresis techniques in harvesting of platelets for transfusion.[3] The introduction of storage at room temperature, the use of

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gas-permeable containers, agitation during storage, and the use of acid citrate as the anticoagulant led to better platelet preservation and increased storage time, allowing widespread availability.[4–6] Platelets have become the second commonest blood components transfused.

PLATELET LIFE SPAN

Circulating platelets have a life span of 10 days and about 10% of platelets are removed every day mainly via the spleen and the liver.[7] What determines the end of platelet life span in the circulation is not known and there are several hypotheses. Phosphatidylserine, a well-known macrophage recognition signal for clearance of apoptotic cells, could play a role.[8–10] In resting platelets, phosphatidylserine is located on the inner leaflet of the membrane bilayer and following platelet activation there is trans-bilayer movement from the inner to the outer leaflet.[11,12] Both an activation-dependent and a senescence-induced pathway leading to a trans-bilayer movement of phosphatidylserine have been described.[13] According to "the multiple-hit model," the life span of platelets is determined by the damages to (or activations of) platelets in the blood circulation. Platelet clearance by macrophages depends on the number of "hits" accumulated during platelet life span in the circulation. Logistic regression analysis of the disappearance curves of labeled transfused platelets by best fitting models suggests a complicated clearance process involving linear (due to senescence) and random (due to activation) components.[14] In recent years, an alternate model, based on forward genetic studies with *N*-ethyl-*N*-nitrosourea–induced mutagenesis in mice, suggests platelets are formed with an "internal clock" and their survival is determined by intrinsic mechanisms rather than external hits.[15] Platelets express the Bcl-2 family of proteins Bax and Bak in the mitochondria.[16–18] These proteins govern mitochondrial outer membrane integrity and can be either pro-apoptotic (Bax, BAD, and Bak among others) or anti-apoptotic (Bcl-x). Knock-out of antiapoptotic Bcl-x(L) reduces platelet half-life and causes thrombocytopenia.[18] Deletion of proapoptotic Bak corrects these defects, and platelets from Bak-deficient mice circulate for a longer time than normal platelets. Apoptotic stimuli are thought to activate BH3-domain–containing members of this protein family to initiate Bax/Bak-dependent apoptosis. ABT737, a synthetic BH3 mimetic reagent, induces the mitochondrial pathway of apoptosis by binding to Bcl-2 and Bcl-XL and blocking their inhibitory effect on the proapoptotic Bax and Bak. ABT737 has been used to mimic in vivo senescence and phosphatidylserine exposure in platelets.[19]

There is evidence for a fixed daily requirement of platelets.[7] A large number of studies have shown that platelets support the function of the vascular endothelium, and in animals thrombocytopenia has been shown to increase protein permeability across the endothelium of the lung, ear, thyroid, and heart, which can be reversed by infusion of platelet-rich plasma.[20–23] These data are also consistent with clinical observations that recovery of transfused platelets is decreased in thrombocytopenia and may account for the spontaneous unprovoked bleeding seen in severe thrombocytopenia. Daily obligatory requirement is estimated to be about 7100/μL, about 18% of daily turnover.

The life span of platelets stored at room temperature is remarkably similar to the life span of platelets in the circulation. Platelet recovery after transfusion decreases by 10% for each day of storage outside of the body, which is very close to what is expected from the in vivo life span of platelets. The changes in stored platelets are collectively known as platelet storage lesions.[24–26] These changes result not only in reduced response to agonists but also in an accelerated clearance from the circulation