Transfusion Medicine Reviews 30 (2016) 230–234

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Current Status of Platelet Transfusion in Pediatric Patients

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ARTICLE INFO

Available online 4 August 2016

Keywords:
Platelet transfusion
Pediatrics
Guidelines

ABSTRACT

Outside the neonatal period, most platelets that are transfused to pediatric patients are given to those who are thrombocytopenic secondary to malignancy and associated therapy and/or hematopoietic progenitor cell transplant, or to those with significant bleeding associated with surgery, especially cardiac surgery. Indications for platelet transfusion, doses, and other practices for children largely mimic adult platelet transfusion protocols because there are few pediatric-specific studies in this area. Pediatric platelet transfusion practices would benefit from focused pediatric research. The appropriate indications and doses for platelet transfusions in oncology, hematopoietic progenitor cell transplant, and cardiac surgery patients need to be determined.

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Platelet transfusions constitute approximately 19% of transfusions to pediatric patients in children's hospitals [1]. Outside the neonatal period, most platelet transfusions are given to children with thrombocytopenia secondary to malignancy and associated therapies and/or hematopoietic progenitor cell (HPC) transplant, or to those with significant bleeding associated with surgery, especially cardiac surgery. Pediatric platelet transfusion practices largely mimic adult platelet transfusion protocols because there are few pediatric specific studies in this area [2]. Surveys of platelet transfusion practices have demonstrated wide variability in practice across institutions and countries [3-6]. In addition, audits of platelet transfusion practice in the United Kingdom showed that 30% to 40% of all platelet transfusions administered were not given in accordance with current recommendations [7].

The prophylactic transfusion of platelets to patients receiving myelosuppressive chemotherapy has been shown to reduce bleeding morbidity. Early practice used a platelet threshold of 20 000/μL to trigger transfusion. This threshold was empirically derived based on the observation that the frequency and severity of hemorrhage were inversely associated with platelet count and more severe when the platelet count was less than 20 000/μL. Although no safe threshold of platelet count was observed, grossly visible hemorrhage rarely occurred when an

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http://dx.doi.org/10.1016/j.tmrv.2016.07.006
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individual's platelet count was greater than 20 000/μL [8-10]. More recently, this transfusion trigger has been decreased to less than 10 000/μL. Children, adolescents, and young adults were included in the initial patient groups from which these transfusion guidelines were developed, but most guidelines pertaining to current platelet transfusion practices were informed by adult studies. The justification for using similar guidelines for both children and adults is based on the similarity between children and adults in "normal" platelet count. However, platelet function may not be identical. When surface expression of physiologically important adhesion receptors is analyzed by flow cytometry, children demonstrate decreased expression of glycoprotein IIb/IIIa (integrin αIIbβ3) on their platelets as of age 2 years, and less β3 is expressed on platelets in children up to age 15 years [11]. In addition, platelets from children of all ages demonstrate a decreased ability to change the conformation of αIIbβ3 to its "activated" form critical for binding of fibrinogen, and exhibit less efficient internalization of glycoprotein Ib/IX upon activation. [11] However, despite these differences in surface receptor expression in platelets noted in children, functional studies (ie, ability to respond to platelet agonists in a flow/shear environment) reveal no differences between platelets from adults and children beyond the newborn period [12,13]. At least 1 analysis has demonstrated an increased incidence of bleeding in pediatric oncology patients as compared with adult patients across a wide spectrum of platelet counts [14]. Consequently, the authors hypothesized that other non–platelet-related factors were the cause for this observed difference.

This review focuses on platelet transfusions in children. Neonatal platelet transfusions are discussed elsewhere in this edition. Consistent with the literature, this review distinguishes prophylactic platelet transfusions administered to prevent bleeding from therapeutic platelet transfusions given to control and stop bleeding.

Current Practice

Use of Prophylactic Transfusions

As early as the 1960s, studies supported the efficacy of prophylactic platelet transfusions administered to patients receiving cancer chemotherapy [8-10,15]. The patients in these studies included children and adolescents in addition to young adults. A platelet threshold of less than 20 000/μL was arbitrarily set as the transfusion trigger based on an observation that serious bleeding rarely occurred with a platelet count above this value. Subsequent studies in adults found safety in using a lower platelet count of 10 000/μL to trigger a platelet transfusion [16]. In aggregate, these studies demonstrated a reduction in hemorrhagic morbidity. Because the older studies that included children often relied on historic controls and many patients received aspirin as an antipyretic, the quality and applicability of these studies to current pediatric practice is questionable.

More recent studies have found that prophylactic platelet transfusions administered for a platelet count less than 10×10^9/L reduced the rate of hemorrhage in adult patients who have undergone HPC transplants or therapy for acute myeloid leukemia compared with no prophylactic transfusions [17,18]. Stanworth et al [17] found World Health Organization (WHO) grade 2 or higher bleeding occurring on 50% of the days for patients who did not receive prophylactic transfusions vs 43% of the days for patients who received prophylactic transfusions. Wandt et al [18] had similar findings, with 42% of patients developing WHO grade 2 or higher bleeding per treatment cycle compared with 19% of patients who received prophylactic transfusions. Although Wandt et al found a lower incidence of bleeding associated with prophylactic transfusions in each patient group including those who received autologous HPC transplants, they argued that autologous HPC patients may not require routine prophylactic platelet transfusions because their overall bleeding rates were lower than those of patients with acute myelogenous leukemia. Although the safety of this recommendation is controversial, the applicability of these data to pediatric autologous HPC transplant patients is even more in question given the potential higher bleeding incidence noted in pediatric HPC patients as compared with adults [14].

Transfusion Threshold

Current pediatric platelet transfusion practice largely mirrors adult practice. If a patient is unable to produce platelets because of either the impact of disease on the bone marrow or the effects of therapy, then a prophylactic platelet transfusion is generally administered when the platelet count is less than 10 000/μL. There is no "target" post-transfusion platelet count for prophylactic platelet transfusions, and consequently, a follow-up platelet count is generally not obtained until the next day. An additional indication for a platelet transfusion is in a patient with a qualitative platelet defect who is to undergo an invasive procedure or who is actively bleeding. However, in contrast to the practice of transfusing platelets in the presence of thrombocytopenia and deficient platelet production, guidelines for the transfusion of platelets to treat bleeding due to a qualitative platelet defect are not universally accepted [2]. In this setting, the baseline platelet count is generally normal and the trigger for a transfusion is unrelated to the platelet count. Case reports suggest that adequate surgical hemostasis can usually be achieved when transfusions increase the platelet by approximately 100 000/μL, although fewer platelets may be adequate when used in combination with factor VIIa and/or tranexamic acid. However, because of a high incidence of alloantibody induction in disorders characterized by deficiencies of platelet surface glycoproteins (ie, Glanzmann thrombasthenia, Bernard-Soulier syndrome), treatment with recombinant factor VIIa for severe bleeding is an additional option to be considered [19,20].

In contrast, if a patient is bleeding and is thrombocytopenic, a therapeutic platelet transfusion may be administered to support hemostasis. Under these conditions, transfusion to achieve a specific platelet count is often the goal. Evidence supporting a specific threshold to trigger a therapeutic platelet transfusion is limited and guidelines often rely on "expert opinion" developed from case series. Although there are no studies comparing no platelet transfusion to platelet transfusion for surgery or the performance of invasive procedures [21], several studies in adults have suggested that a platelet count of 20 000/μL is sufficient for placement of a central venous catheter, whereas a platelet count of 50 000/μL is recommended for a lumbar puncture (LP) [22,23]. A single retrospective case series in children concluded that a central venous catheter can safely be placed when the platelet count is at least 50 000/μL [24]. Other retrospective studies have found that LPs can be safely performed in thrombocytopenic patients. Although the incidence of traumatic LPs with greater than 500 erythrocytes per high-power field increases with lower platelet counts [25], Howard et al. [26] reported that no serious complications occurred in a retrospective analysis of 5223 LPs performed on children, including 199 patients with platelet counts less than 20 000/μL. Based on their data, Howard et al recommended that platelet transfusions are unnecessary before LPs in children whose platelet count is greater than 10 000/μL. A retrospective report in adults did not demonstrate any reduction in red blood cell transfusions after surgery in patients who received a prophylactic platelet transfusion preoperatively [27].

Platelet Dose

The platelet selection and preparation methods used are generally identical for pediatric and adult patients, with the exception that smaller doses are prepared for pediatric patients. The doses usually are close to the dose per kilogram of body weight administered to adult patients. Some of the early studies that reported on the efficacy of prophylactic transfusions also investigated the dosing administered to patients receiving cancer chemotherapy [8-10,15]. In general, no added benefit (in regard to bleeding episodes) was noted with the transfusion of a

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