LOWERING THE STANDARD DOSE OF PLATELETS: IS THE TIMING RIGHT FOR THE U.S.?

By Mark T. Friedman, DO
NYU Langone Health
NYU Grossman Long Island School of Medicine
Mineola, NY

It has been 13 years since Slichter et al published results from the Platelet Dose (PLADO) study, the 2010 landmark research examining randomly assigned hospitalized patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumors who received prophylactic low-, medium- or high-dose platelet transfusions.1 Although the study’s data demonstrated that the number of platelets in a prophylactic transfusion did not affect the patient’s risk of bleeding, the required standard number of platelets in an apheresis unit in the United States has remained unchanged at 3.0 x 10\(^{11}\) (equivalent to a platelet dose of 2.2 x 10\(^{11}\)/m\(^2\) body surface area for a typical 70 kg adult). But is now an appropriate time to consider lowering the recommended platelet dose? While some may dismiss the PLADO study results as not generalizable to most patients, given the narrow scope of enrolled participants and the lack of studies reporting on platelet dosing in other patient groups, others think they should be considered for a broader population.

A CLOSER LOOK AT THE U.S. PLATELET DOSE AND USAGE

First, let us consider the challenges with the current U.S. standard platelet dose. For starters, the current 3.0 x 10\(^{11}\) per apheresis unit standard was initially set by the Food and Drug Administration more than 50 years ago, when apheresis technology was emerging in the early 1970s. The standard was not based on data from studies demonstrating clinical effectiveness, but merely on the average number of platelets in a pool of six platelet concentrates derived from whole blood, which was the standard for platelet transfusion at the time.2 In addition, this standard platelet dose is higher than the dose used in Canada and most European Union nations, which range from 2.0 to 2.5 x 10\(^{11}\) per apheresis unit.2

What would be the potential key advantages of lowering the platelet dose in the U.S.? There are several benefits to consider. Benjamin et al., who argue for lowering the dose, point out that the U.S., with approximately 2 million platelet transfusions per year (primarily for prophylactic use to prevent bleeding episodes) has the highest per capita use of platelets in the world (Figure 1).3,4 The vast majority of these transfusions (90-95%) involve apheresis platelets, which have become the preferred platelet product in the U.S. because of higher platelet yields, reduced donor exposures and a reduced risk of bacterial contamination associated with apheresis units vs. whole-blood derived
concentrate pools. As a result of this relatively high utilization, along with the fact that platelets have a short shelf-life, there is a constant strain on the platelet supply such that shortages have become commonplace. According to Benjamin et al., lowering the required platelet dose could increase platelet units up to 23% without changing collection procedures since it would qualify more donor collections to be split into multiple units. Yet, Benjamin et al. caution that triple platelet collections have been associated with longer platelet collection times and a higher risk for bacterial contamination, indicating that lowering the dose could potentially compromise transfusion safety and donor comfort. Current bacterial risk control strategies, including the use of large volume-delayed sampling (LVDS) platelets and increased use of pathogen-reduced (PR) platelets, were initially made possible by the 2021 FDA guidance on bacterial risk control strategies for platelet transfusions to mitigate the risk of bacterial contamination. Additional processing of platelets to comply with the FDA guidance – whether LVDS or PR – in addition to the use of alternative storage media such as platelet additive solutions (PAS), may result in increased collections of low-yield (i.e., < 3.0 x 10\(^11\)/unit) apheresis platelets. Benjamin et al. found that increasing use of these lower yield products may not correlate with increased transfusion rates, as would be expected, since France and Switzerland, for example, have lower platelet dose requirements (2.0 x 10\(^11\) and 2.4 x 10\(^11\), respectively) but lower per capita use than the U.S. (Figure 1) The French and Swiss experience with these components (i.e., PR platelets collected in PAS) has not been associated with an increased risk for excessive bleeding. Nevertheless, Benjamin et al. concede that smaller platelet transfusion dosing may lead to shorter intertransfusion intervals and an increased number of transfusions for inpatients in the U.S., which could increase the workload for the transfusion service and nursing staff. However, their analysis of the PLADO data suggests that this effect would likely be minimal. Labeling apheresis platelets with the actual platelet content, as required for low-yield platelets in the U.S., could also help to improve targeted dosing.

**ASSESSING THE CURRENT SITUATION**

Is the U.S. currently in a position to accept lower platelet doses? While this movement has strong proponents, the answer, probably, is “not now.” For one, as noted, the only major research published to date assessing platelet dose is the PLADO study, which is limited in scope to a small subset of hospitalized patients receiving prophylactic platelet transfusions. While we could accept clinical experience from Europe and Canada as evidence for efficacy, this may not be enough to convince the FDA to lower the current standard.

In their analysis of strategies to expand the platelet inventory to mitigate the impact of severe shortages, Stubbs et al. proposed four approaches that could strengthen donor recruitment and improve utilization and the inventory:

- Use of paid donors
- Continued efforts toward production of buffy coat [whole blood-derived] platelets
- Improved logistics to (re)distribute platelets for optimal usage
- Use of cold-stored platelets
These authors acknowledge reduced platelet dosage as an additional initiative, but it was not their focus. Yet, using paid donors is even more unconventional than reducing the platelet dosage. Therefore, lowering the dose may be the most reasonable and achievable measure toward improving platelet inventory management and utilization in the U.S. While additional studies would likely provide more evidence for this effort, the dosing restrictions may ultimately be lowered out of critical necessity arising from another prolonged disaster such as the COVID-19 pandemic. Toward that end, both blood centers and hospital transfusion services may need to take the matter upon themselves and provide split products to support ongoing patient needs during a potential future crisis.

AABB published platelet transfusion guidelines in 2015, recommending prophylactic transfusions for thrombocytopenic patients when the platelet count reaches $10 \times 10^9$/L or less to reduce the risk of spontaneous hemorrhage, $20 \times 10^9$ or less for elective central venous catheter placement, and $50 \times 10^9$/L or less for elective diagnostic lumbar puncture (LP) or major elective nonneuraxial surgery. These recommendations were primarily based on expert opinion and low-quality evidence; today, adherence to these guidelines is somewhat limited and clinical practices can vary widely. For example, a popular resource recommends not performing LP when platelet counts are below 50,000 to 80,000/µL, meaning that physicians consulting this particular resource are apt to transfuse multiple units of platelets to reach a count at the upper limit of the recommendation (i.e., 80,000/µL), a situation that could be exacerbated by lowering the dose in each unit. Furthermore, the AABB guidelines do not specifically address platelet transfusions for neurosurgery, whereby the generally accepted threshold is a platelet count of 100,000/µL, again based on expert opinion in the face of a lack of sufficient data. Will clinicians accept transfusing their patients with lower platelet doses? This is an even more challenging issue than whether or not the FDA may consider lowering the recommended dose in the first place.


Figure 1: Units of platelets transfused per 1000 population in countries grouped by World Health Organization (WHO) regions