Response to random apheresis platelets versus HLA-selected platelets versus pooled platelets in HLA-sensitized patients

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BACKGROUND: It is unknown how pooled platelets (PPs) compare to random apheresis platelets (RAPs) when HLA-selected platelets (PLTs) are unavailable for HLA-sensitized patients. The aim of this study was to compare patient responses to RAPs, HLA-selected PLTs, and PPs in HLA-sensitized patients.

STUDY DESIGN AND METHODS: This is a single-institution retrospective study of patients from January 2014 to April 2017 with a class I calculated panel-reactive antibody of 60% or more. Response to transfusion was determined by a corrected count increment (CCI) up to 1 hour after completion of transfusion. A CCI of 5 or more was considered successful.

RESULTS: Seventy-seven units of RAPs, 412 units of HLA-selected PLT, and 388 units PPs were transfused. Mean CCIs when transfusing RAPs, HLA-selected PLTs, and PPs were 2.82, 11.44, and 4.77, respectively ($p < 0.0001$). Posttest comparison between RAPs and PPs revealed no significant difference in mean CCI while there was a significant difference between HLA-selected PLTs versus RAPs and HLA-selected PLTs versus PPs. The success rates of RAPs, HLA-selected PLTs, and PPs were 31%, 80%, and 35% respectively. There was no significant association of type of PLT and success rate when comparing RAPs versus PPs ($p = 0.51$) while there was a significant association between success rate and type of PLT transfusion when comparing HLA-selected PLTs with RAPs and PPs.

CONCLUSION: HLA-selected PLTs resulted in higher mean CCIs and more successful transfusions. There was no significant difference in mean CCI or success rate when transfusing RAPs versus PPs to HLA-sensitized patients. Future studies should assess clinical outcomes in HLA-sensitized patients receiving each type of PLT product.

Refractoriness to platelet (PLT) transfusions has been associated with poor outcomes.[1] Although non-immune factors such as splenomegaly, sepsis, medications, bleeding, or disseminated intravascular coagulation (DIC) contribute more often to PLT transfusion refractoriness, immune causes such as human leukocyte antigen (HLA) Class I alloimmunization still remain an important cause of refractoriness.[2] For patients with HLA Class I alloantibodies, various methods exist to select the product that will increase the chances of an adequate posttransfusion count. Some institutions provide crossmatch-compatible PLTs while other centers use previously typed PLT donors to either select units that are negative for the antigen for which the patient has antibodies against (i.e., HLA avoidance) or select units that are matched to the patient's own HLA type (i.e., HLA matched).[3]

Both crossmatch-compatible PLTs and HLA-selected PLTs (HLA avoidance or HLA matched) may not always be available in a timely manner. In this instance, one option is to transfuse pooled PLTs (PPs), derived from four to six whole blood donations. Hypothetically, one or more of the PLT concentrates in the pool may be negative for the antigen against which the patient has antibodies.[4] It is unknown whether PPs provide an advantage over random apheresis PLTs (RAPs) for patients with HLA Class I antibodies and how this compares to HLA-selected

ABBREVIATIONS: cPRA = calculated panel-reactive antibody; PP(s) = pooled platelet(s); RAP(s) = random apheresis platelet(s).

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PLTs. The aim of our study was to compare the response to transfusion of RAPs versus HLA-selected PLTs versus PPs in HLA-sensitized patients.

MATERIALS AND METHODS

Patient selection

We conducted a retrospective study of all patients at a single academic institution who had a calculated panel-reactive antibody (cPRA) performed between January 2014 and April 2017. Patients were included if the cPRA was 60% or more. Due to the retrospective nature of the study, informed consent was not sought for the use of patient data. The University of Washington Institutional Review Board approved the study.

PLT product selection

After a patient was identified to be refractory to PLT transfusion, a cPRA was ordered. HLA antibody testing was performed at the regional blood center using a Luminex-based assay (One Lambda) as previously described.[3] If the class I cPRA was 60% or more, HLA-selected PLTs were ordered. Patients were often supported with PPs until HLA-selected PLTs were available. All PLT products were supplied by the regional blood center. PPs were prepared by the PLT-rich plasma method from four to six whole blood donors. HLA-selected PLTs included both PLTs that were antigen negative (HLA avoidance) as well as PLTs that were matched to the patient's own HLA A and B phenotype (HLA matched). Information on the grade of matching (i.e., A, B1U, B1U, B2UX) was not available. None of the PLTs in the study were pathogen reduced.

Data extraction

From the electronic medical record, we recorded patient sex, age, date of cPRA sample collection, cPRA level, primary diagnosis, presence of splenomegaly, body surface area, ABO blood type of the patient, PLT unit numbers, and 1-hour corrected count increments (CCIs). From the blood bank laboratory information system, we gathered information on type of PLT (RAPs vs. HLA-selected PLTs vs. PPs), ABO type of the PLT unit, and whether the unit was volume reduced (the standard process includes removing plasma to have a final product of 100 mL) or washed. The age of the PLT unit was not available for analysis.

Response to PLT transfusion

Response to PLT transfusion was measured by the 1-hour CCI:

CCI = [(Posttransfusion PLT count within 1 hr of completion of transfusion – pretransfusion PLT count) × body surface area]/number of PLTs transfused.

We defined a successful PLT transfusion as a CCI of 5.0 or more.[5] We used the annual median PLT counts for RAPs, HLA-selected PLTs, and PPs based on the local blood center internal quality control testing. For PLTs that were volume reduced or washed, the number of PLTs transfused was multiplied by 80% and 70%, respectively.[6] We only included PLT transfusions that occurred within 3 days before and up to 31 days after cPRA sample collection (defined as an encounter). PLT transfusions in which incomplete information was entered in the patient's chart (e.g., unit number not documented correctly, unknown type of PLT, or no 1-hr postcount) were excluded from the analysis. Transfusions that were not fully completed or instances where more than 1 PLT unit was transfused before the next posttransfusion count were also excluded.

Statistical analysis

Categorical data are described as counts and percentages, and continuous variables are expressed as medians (range) and means (± standard deviation [SD]). Comparison of mean CCIs among RAPs versus HLA-selected versus PPs were performed using the Kruskal-Wallis test with Dunn's multiple comparisons test as the posttest. Comparison of median CCIs between ABO major/bidirectional incompatibility versus identical/minor incompatibility were made using the Mann-Whitney U test for nonparametric data. Associations of categorical variables were calculated with the Fisher's exact test (comparing two groups) or chi-square analysis (comparing more than two groups).

We decided a priori to analyze two subgroups of patients: 1) patients who received at least 1 unit of each RAPs, HLA-selected PLTs, and PPs and 2) those who received at least 1 unit of each RAPs and PPs within the same encounter. Paired mean CCIs per patient in this first subgroup were compared using Friedman's test with Dunn's multiple comparisons posttest. Paired mean CCIs per patient in the second subgroup were compared with Wilcoxon matched-pairs signed-ranks test. All data were recorded in a computer spreadsheet (Microsoft Excel, Microsoft Corp.) and analyzed with computer software (GraphPad InStat V3.10, GraphPad Software).

RESULTS

Patient characteristics

Ninety-four patients received 877 PLT transfusions with 1-hour CCIs available (Table 1). Eighty-two were female (87%), and the median (range) age at time of their first cPRA was 55 (20-84) years. Median (range) class I cPRA was 90% (60%-100%). Splenomegaly was confirmed by radiological imaging in 26 patients (27.7%). The most common primary diagnosis was acute leukemia (50% of patients).

PLT transfusion characteristics

Seventy-seven units of RAPs, 412 units HLA-selected PLTs, and 388 units of PPs were transfused to 41, 60, and 81 patients, respectively (Table 2). There was no significant association between type of PLTs transfused and whether the patient had splenomegaly ($p = 0.12$). There was a significant association between type of PLTs transfused and ABO compatibility of the PLT transfusion ($p < 0.0001$). HLA-selected PLTs were more often ABO major or bidirectionally incompatible (35.9%) compared to RAPs (16.9%)

TABLE 1. Patient characteristics

Number of patients	94
Sex (males/females)	12/82
Age (years) at first cPRA, median (range)	55 (20-84)
class I cPRA, median (range)	90% (60%-100%)
Splenomegaly	
No splenomegaly	44 (46.8%)
Splenomegaly	26 (27.7%)
Unknown	24 (25.5%)
Primary diagnosis	
Acute leukemia	47 (50%)
Myelodysplastic syndrome	17 (18.1%)
Cirrhosis	6 (6.4%)
Plasma cell neoplasm	6 (6.4%)
Aplastic anemia	5 (5.3%)
Other	13 (13.8%)

and PPs (20.9%). This association remained significant when comparing RAPs and HLA-selected PLTs ($p < 0.001$) and PPs and HLA-selected PLTs ($p < 0.001$) but not when comparing RAPs and PPs ($p = 0.53$). There was also a significant association between type of PLT transfused and patient class I cPRA ($p = 0.02$) with HLA-selected PLTs more likely to be transfused to patients with a class I cPRA of 81% to 100%. This association only remained significant when comparing HLA-selected PLTs versus PPs ($p < 0.01$). Overall, the median (range) time between the pre-transfusion PLT count and the start of PLT transfusion was 1.28 (0.00-46.57) hours.

Response to PLT transfusion

We first sought to evaluate the response to each PLT transfusion. The mean (±SD) CCIs per PLT transfusion when using RAPs, HLA-selected PLTs, and PPs were 2.82 (±5.82), 11.44 (±8.12), and 4.77 (±6.93), respectively (Table 3). The median (range) CCIs per PLT transfusion when using RAPs, HLA-selected PLTs, and PPs were 0.89 (−9.72 to 20.34), 10.09 (−5.51 to 47.53), and 2.60 (−16.66 to 46.55), respectively. There was a significant difference when comparing all three mean CCIs per PLT transfusion ($p < 0.0001$), when comparing RAPs versus HLA-selected PLTs ($p < 0.001$) and when comparing HLA-selected PLTs versus PPs ($p < 0.001$). There was no significant difference when comparing RAPs versus PPs ($p > 0.05$).

We then sought to evaluate the response from each patient to the different PLT products. The mean (±SD) CCIs per patient when receiving RAPs, HLA-selected PLTs, and PPs were 2.82 (±5.93), 13.92 (±7.64), and 4.46 (±5.16), respectively (Table 3). There was a significant difference when comparing all three mean CCIs per patient ($p < 0.0001$), when comparing RAPs versus HLA-selected PLTs ($p < 0.001$), and when comparing HLA-selected PLTs versus PPs ($p < 0.001$). There was no significant difference when comparing RAPs versus PPs ($p > 0.05$).

Next, we evaluated the success rate per PLT product. The rates of successful transfusion when receiving RAPs, HLA-selected PLTs, and PPs were 31%, 80%, and 35% respectively (Table 3). There was a significant association between type of PLTs transfused and success rate ($p < 0.0001$). This association remained significant when comparing RAPs and HLA-selected PLTs ($p < 0.0001$) and PPs and HLA-selected PLTs ($p < 0.0001$). There was no significant association between success rate and type of PLT transfused when comparing RAPs and PPs ($p = 0.51$).

Finally, we evaluated how ABO compatibility of the PLTs affected response. Overall, there was no significant difference ($p = 0.36$) between the median CCIs of ABO major/bidirectional incompatibility versus ABO identical/minor incompatibility. On subgroup analysis, there was no significant difference between median CCIs of RAP ABO major/bidirectional incompatibility versus RAP ABO identical/minor incompatibility ($p = 0.18$). There was also no significant difference between median CCIs of PP ABO major/bidirectional incompatibility versus PP ABO identical/minor incompatibility ($p = 0.47$). However, there was a significant difference ($p = 0.02$) between median (range) CCIs of HLA ABO major/bidirectional incompatibility (8.84, −0.78 to 35.3) versus HLA ABO identical/minor incompatibility (10.81, −1.04 to 47.53).

Subgroup 1: patients who received at least one of RAPs, HLA-selected PLTs, and PPs

Twenty-two patients received at least 1 unit of RAPs, HLA-selected PLTs, and PPs (Table 4). Forty-five units of RAPs, 155 HLA-selected PLTs, and 148 PPs were transfused to the 22 patients. Mean (±SD) CCIs per patient when receiving RAPs, HLA-selected PLTs, and PPs were 1.83 (±4.93), 10.77 (±6.40), and 3.61 (±5.07), respectively. Median (range) CCIs

TABLE 2. PLT transfusion characteristics

	RAPs	HLA-selected PLTs	PPs
Number of PLT units transfused	77	412	388
Transfused to a patient with confirmed splenomegaly*	30 (38.9%)	172 (41.7%)	134 (34.5%)
ABO major/bidirectional incompatibility†	13 (16.9%)	148 (35.9%)	81 (20.9%)
Transfused to a patient with cPRA of 81%-100%‡	48 (62.3%)	285 (69.2%)	233 (60.1%)

* No significant association.

† $p < 0.0001$ when comparing all three types of PLTs together. This association only remained significant when comparing RAPs versus HLA-selected PLTs ($p < 0.001$) and PPs versus HLA-selected PLTs ($p < 0.001$).

‡ $p < 0.02$ when comparing all three types of PLTs together. This association only remained significant when comparing PPs versus HLA-selected PLTs ($p < 0.01$).

TABLE 3. Response to PLT transfusion

	RAPs	HLA-selected PLTs	PPs
Number of PLT units transfused	77	412	388
CCI per PLT unit			
Mean (±SD)*	2.82 (±5.82)	11.44 (±8.12)	4.77 (±6.93)
Median (range)	0.89 (−9.72 to 20.34)	10.09 (−5.51 to 47.53)	2.60 (−16.66 to 46.55)
Number of patients receiving each type of PLT †	41	60	81
CCI per patient, mean (±SD)	2.82 (±5.93)	13.92 (±7.64)	4.46 (±5.16)
Successful transfusions‡	24 (31%)	330 (80%)	136 (35%)

* $p < 0.0001$ when comparing all three mean CCIs. This difference remained significant when comparing RAPs versus HLA-selected PLTs ($p < 0.001$) and PPs versus HLA-selected PLTs ($p < 0.001$) but not when comparing RAPs versus PPs ($p > 0.05$).
† $p < 0.0001$ when comparing all three mean CCIs per patient. This difference remained significant when comparing RAPs versus HLA-selected PLTs ($p < 0.001$) and PPs versus HLA-selected PLTs ($p < 0.001$) but not when comparing RAPs versus PPs ($p > 0.05$).
‡ $p < 0.0001$ when comparing success rate of all three types of PLTs. This association remained significant when comparing RAPs versus HLA-selected PLTs ($p < 0.0001$) and PPs versus HLA-selected PLTs ($p < 0.0001$) but not when comparing RAPs versus PPs ($p = 0.51$).

per patient when receiving RAPs, HLA-selected PLTs, and PPs were 0.20 (−3.56 to 19.74), 9.59 (2.70 to 26.00), and 2.57 (−1.04 to 20.38), respectively. There was a significant difference when comparing all three paired mean CCIs per patient ($p < 0.0001$), when comparing RAPs versus HLA-selected PLTs ($p < 0.001$), and when comparing HLA-selected PLTs versus PPs ($p < 0.001$). There was no significant difference when comparing RAPs versus PPs ($p > 0.05$).

Subgroup 2: patients who received at least 1 unit of RAPs and PPs within the same encounter

Thirty-six patients received at least 1 unit of RAPs and PPs within the same encounter (Table 5). This includes the 22 patients from Subgroup 1 in addition to 14 other patients who received at least 1 unit of RAPs and PPs but no HLA-selected PLTs. Sixty-eight units of RAPs and 177 units of PPs were transfused to the 36 patients. Mean (±SD) CCIs per patient when receiving RAPs and PPs were 2.74 (±6.00) and 3.71 (±5.95), respectively, and median (range) CCIs per patient were 0.63 (−8.29 to 20.34) and 2.06 (−1.06 to 26.36) for RAPs and PPs, respectively. There was no significant difference when comparing paired mean CCIs per patient when receiving RAPs and PPs ($p = 0.26$). Fig. 1 displays the individual mean CCI per each patient when receiving RAPs and PPs. Of the 36 patients, 16 patients had a mean CCI of not more than 5 to both RAPs and PPs and had also received at least 1 HLA-selected PLT unit during the study period. Of these 16 patients, 14 (87.5%) had a mean CCI of 5 or more when receiving HLA-selected PLTs. Additionally, five patients had mean CCIs of 5 or more when receiving both RAPs and PPs. Only one of these patients received HLA-selected PLTs during the study period. They had an adequate response to HLA-selected PLTs as well.

TABLE 4. Patients who received at least 1 unit of RAPs, HLA-selected PLTs, and PPs: PLT response

	RAPs	HLA-selected PLTs	PPs
Number of PLT units transfused	45	155	148
Number of patients receiving each type of PLT	22	22	22
CCI per patient			
Mean (±SD)*	1.83 (±4.93)	10.77 (±6.40)	3.61 (±5.07)
Median (range)	0.20 (−3.56 to 19.74)	9.59 (2.70 to 26.00)	2.57 (−1.04 to 20.38)

* $p < 0.0001$ when comparing all three paired mean CCIs per patient. This difference remained significant when comparing RAPs versus HLA-selected PLTs ($p < 0.001$) and PPs versus HLA-selected PLTs ($p < 0.001$) but not when comparing RAPs versus PPs ($p > 0.05$).

DISCUSSION

In this retrospective review of HLA-sensitized patients, HLA-selected PLTs resulted in greater mean CCIs per transfusion, mean CCIs per patient, and more successful transfusions than both RAPs and PPs. This difference was despite the fact that the HLA-selected PLTs were more likely to be transfused to patients with a cPRA of 81% to 100% and more likely to have been ABO incompatible, which has been associated with decreased PLT increments.[7–9]

It should be expected that HLA-selected PLTs would be superior to either RAPs or PPs. A recent systematic review found that HLA-selected PLTs do result in greater 1-hour CCIs compared to randomly selected PLTs.[10] However, some previous studies have demonstrated conflicting results with the use of

TABLE 5. Patients who received at least 1 unit of RAPs and PPs within the same encounter: PLT response

	RAPs	PPs
Number of PLT units transfused	68	210
Number of patients receiving each type of PLT	36	36
CCI per patient		
Mean (±SD)*	2.74 (±6.00)	3.71 (±5.95)
Median (range)	0.63 (−8.29 to 20.34)	2.06 (−1.06 to 26.36)

* No significant difference in paired mean CCIs.

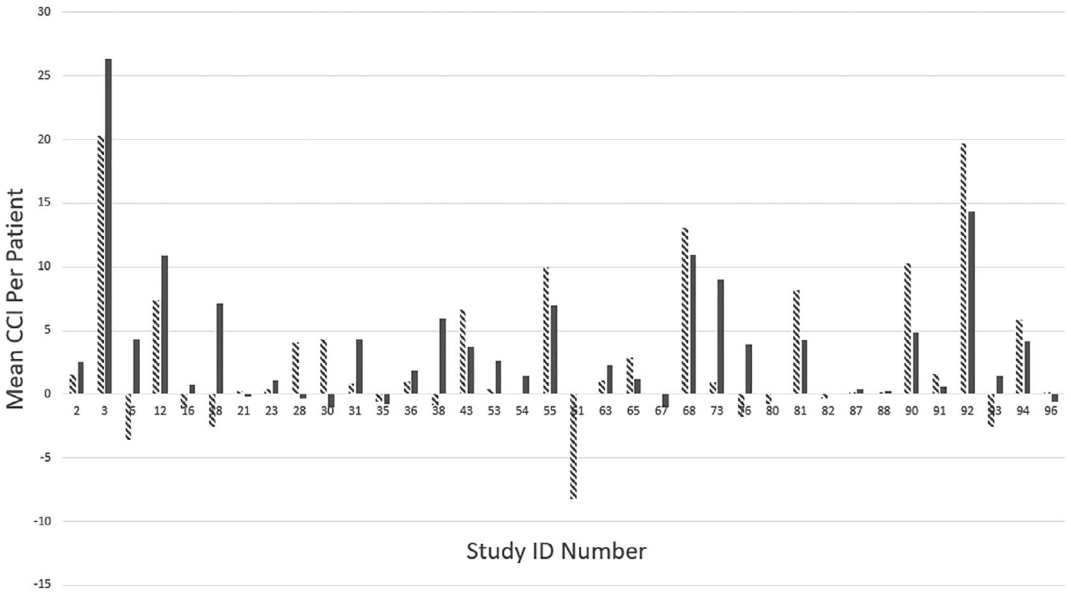

Fig. 1. Patients who received at least 1 unit of RAPs (▨) and PPs (■) within the same encounter: mean CCI per patient.

HLA-selected PLTs.[11] In contrast to the median CCI of 10.09 and 80% success rate with the use of HLA-selected PLTs in this study, a recent retrospective analysis described only a median CCI of 1.2 and 29% success rate with the use of HLA-matched PLTs and did not find a significant difference in the number of successful transfusions when compared to non–HLA-matched PLTs.[11] This substantial difference in median CCI and success rate may be due to the use of a 4-hour CCI instead of 1-hour CCI, degree of HLA matching, and nonimmune clinical factors impacting the majority of PLT transfusions in their study.

There was no significant difference between RAPs and PPs with regard to mean CCIs per PLT unit, mean CCIs per patient, or rate of successful transfusions. A similar pattern of results was observed in the two subgroup analyses. The hypothetical benefit of PPs over RAPs in HLA-sensitized patients was not observed in our study. This may possibly be due to the fact that the majority of patients in our study had a class I cPRA of 81% to 100%. In these highly sensitized patients, we would expect 0% to 20% of the PLTs in the pool to be compatible with the patients. It is possible this low percentage of compatible PLTs is not enough to achieve a CCI of 5 or more. Moreover, our study may not have been adequately powered to discover a significant difference between RAPs and PPs.

Interestingly, there were five patients who responded adequately to both RAPs and PPs despite having cPRAs of 60% or more (Fig. 1). A cPRA may have been ordered for these patients in the context of planning for an allogeneic bone marrow transplant as opposed to PLT refractoriness. This suggests the mere presence of HLA antibodies, as tested by the single antigen bead assay, does not necessarily result in PLT refractoriness. A recent longitudinal study of a subset of patients in the Trial to Reduce Alloimmunization to Platelets (TRAP) study demonstrated that weak to moderate HLA antibody levels are not necessarily associated with PLT refractoriness.[12] In addition, although 45% of patients within the control group of the TRAP study developed HLA antibodies, only 13% of them were considered refractory to PLT transfusions.[5] Similarly, it is possible that the patients in our study who were not refractory also had weak to moderate HLA antibody levels, or they had other patient-related or antibody-related factors that did not result in refractoriness. It is also possible that the PLT units these patients received happened to be negative for the incompatible HLA Class I antigens or expressed HLA Class I antigens at a low level.[13] It is unclear why one of these patients also had HLA-selected PLTs ordered despite having adequate responses to both RAPs and PPs. This emphasizes the importance of only ordering HLA-selected PLTs if there is both an elevated cPRA and clinical evidence of PLT refractoriness unlikely to be due to more common causes of refractoriness.

Aside from the inherent shortcomings of retrospective studies, the primary limitation of our study is the inability to assess clinical outcomes. PLTs are transfused to either prevent or treat bleeding.[14] We were unable to determine the clinical effectiveness of RAPs versus HLA-selected PLTs versus PPs in HLA-sensitized patients. In previous studies, greater CCIs do not necessarily reflect appreciably improved hemostasis[9,15]; thus, it remains imperative to determine what product actually leads to better clinical outcomes. Another limitation of our study includes the lack of information regarding the age of the PLT unit. Previous studies have demonstrated lower CCIs the longer the PLTs are stored.[16] This would not affect the comparison between RAPs and PPs because our transfusion service

issues the oldest RAPs or PPs first (first in, first out) so the storage duration would affect RAPs and PPs equally. The age of the PLTs may have an effect on the comparisons of HLA-selected PLTs as these units were specially chosen and likely slightly fresher than either RAPs or PPs. However, the striking difference in CCIs between HLA-selected PLTs and either RAPs or PPs is unlikely to be entirely due to the age of the PLT unit alone. Finally, we were unable to determine whether other causes of PLT refractoriness such as sepsis, disseminated intravascular coagulation, medications, and so forth affected results. These confounders may have contributed to the difference in mean CCI per PLT when receiving HLA-selected PLTs compared to RAPs and PPs. However, these confounders would not affect the paired comparisons per patient (Subgroups 1 and 2) because the confounders would affect the mean CCI per patient when receiving each type of PLT equally. Given that the results in the subgroup analyses were similar to the overall analyses, it is unlikely that other causes of PLT refractoriness had a significant impact on the overall results of the study. Finally, there were likely some patients with an elevated cPRA excluded from the analysis because a cPRA was never checked due to the patient not being refractory (possibly due to low-level HLA antibodies as stated above). However, this would not confound the data because if they were deemed to not be refractory, then presumably they would respond either slightly better to RAPs or equally as well to RAPs and PPs as demonstrated by prior studies.[17]

In conclusion, HLA-selected PLTs resulted in greater CCIs and more successful transfusions compared to RAPs and PPs. If HLA-selected PLTs are unavailable, our data suggest that RAPs and PPs can be considered equivalent with respect to response to PLT transfusion. Future studies should assess clinical outcomes when HLA-sensitized patients with PLT refractoriness receive each type of PLT product.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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