Transfusion-related adverse events in the Platelet Dose study

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BACKGROUND: How platelet (PLT) product characteristics such as dose, source (whole blood derived [WBD] vs. apheresis), storage duration, and ABO matching status affect the risks of transfusion-related adverse events (TRAEs) is unclear. Similarly, more information is needed to define how recipient characteristics affect the frequency of TRAEs after PLT transfusion.

STUDY DESIGN AND METHODS: In the multicenter Platelet Dose ("PLADO") study, pediatric and adult hematology-oncology patients with hypoproliferative thrombocytopenia were randomized to receive low-dose (LD), medium-dose (MD), or high-dose (HD) PLT prophylaxis for a pretransfusion PLT count of not more than 10×10^9/L. All PLT units (apheresis or WBD) were leukoreduced. Post hoc analyses of PLADO data were performed using multipredictor models.

RESULTS: A total of 5034 PLT transfusions to 1102 patients were analyzed. A TRAE occurred with 501 PLT transfusions (10.0%). The most common TRAEs were fever (6.6% of transfusions), allergic or hypersensitivity reactions (1.9%), and sinus tachycardia (1.8%). Patients assigned HD PLTs were more likely than LD or MD patients to experience any TRAE (odds ratio for HD vs. MD, 1.50; 95% confidence interval, 1.10-2.05; three-group comparison $p = 0.02$). PLT source and ABO matching status were not significantly related to overall TRAE risk. Compared to a patient's first PLT transfusion, subsequent PLT transfusions were less likely to have a TRAE reported, primarily due to a lower risk of allergic or hypersensitivity reactions.

CONCLUSION: The most important PLT unit characteristic associated with TRAEs was PLT dose per transfusion. HD PLTs may increase the risk of TRAEs, and LD PLTs may reduce the risk.

Prophylactic platelet (PLT) transfusions are routinely used to prevent bleeding in patients with hypoproliferative thrombocytopenia resulting from chemotherapy or hematopoietic stem cell transplantation (SCT). The current standard is to

ABBREVIATIONS: BSA = body surface area; HD = high dose; LD = low dose; MD = medium dose; PLADO study = Platelet Dose study; SCT = stem cell transplantation; TRAE(s) = transfusion-related adverse event(s); WBD = whole blood derived.

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administer prophylactic PLT transfusions for a PLT count below 10×10^9/L. PLT transfusion has a number of known risks, both infectious and noninfectious. We hypothesized that PLT product characteristics such as dose, source (i.e., whole blood derived [WBD] vs. apheresis), ABO matching, and storage duration as well as recipient characteristics might affect the frequency of adverse events after PLT transfusion. To investigate these issues, we performed a secondary analysis of data collected during the Platelet Dose (PLADO) study.[1]

The PLADO study[1] was a multicenter randomized controlled trial that examined the effects of prophylactic PLT dose on bleeding in hematology-oncology patients with hypoproliferative thrombocytopenia. Patients in the PLADO trial were randomly assigned to one of three study arms: medium-dose (MD), high-dose (HD), or low-dose (LD) PLTs per transfusion for prophylactic transfusions, which were given when the morning PLT count was not more than 10×10^9/L. The primary outcome of the PLADO study was the percentage of patients with WHO Grade 2 or higher bleeding events.[2] As reported,[1] this outcome was observed in 69, 71, and 70% of patients in the MD, LD, and HD groups, respectively (no significant differences between groups). The LD group patients received transfusions significantly more often, receiving a median of five PLT transfusions each, versus a median of three PLT transfusions each for both the MD and the HD group patients ($p < 0.001$).

We examined how frequently transfusion-related adverse events (TRAEs) were reported in the PLADO study and whether the risk of TRAEs varied depending on PLT characteristics (dose, source, ABO matching status, and storage duration), number of PLT transfusions received to date, or patient characteristics (sex, age group, and type of transplant or chemotherapy).

MATERIALS AND METHODS

The PLADO study was a multicenter randomized controlled trial conducted by the NHLBI Transfusion Medicine/Hemostasis Clinical Trials Network. The study population was composed of pediatric and adult patients with hypoproliferative thrombocytopenia secondary to allogeneic or autologous hematopoietic SCT or chemotherapy for solid or hematologic malignancies. Patients were randomly assigned to one of three different prophylactic PLT dosing strategies. MD PLT transfusions (2.2×10^{11} PLTs/m^2 body surface area [BSA]) approximated the usual dose per prophylactic PLT transfusion currently administered. HD PLT transfusions (4.4×10^{11} PLTs/m^2) represented twice the MD, while LD PLT transfusions (1.1×10^{11} PLTs/m^2) represented half the MD. Randomization was stratified according to four treatment strata (allogeneic hematopoietic SCT, autologous or syngeneic SCT, chemotherapy for solid tumor, or chemotherapy for hematologic cancer) and balanced within each hospital.[3]

For each patient, the data coordinating center communicated to the blood bank the assigned PLT dose and the ±25% allowable range but not the patient's study group. The patient, patient's physician, clinical staff and research staff were not informed of the assigned study group. The patient's physician could change the prophylactic transfusion trigger or dose based on clinical indications, with a return to study parameters as soon as possible. PLTs could be given at any time to treat active bleeding, or in association with an invasive procedure. Patients diagnosed with PLT refractoriness could be switched to HLA-matched PLTs. HLA-matched PLT units were transfused in their entirety to avoid PLT wastage, independent of the patient's study dose assignment.

PLT products were either apheresis or pooled WBD PLT concentrates prepared by the PLT-rich plasma method. PLTs were stored under standard conditions (20-24°C with continuous agitation) for up to 5 days, except for a brief interval in which the FDA-permitted 7-day storage for apheresis PLTs only. Apheresis PLTs were leukoreduced before storage, while WBD PLTs were leukoreduced after storage before transfusion. PLT ABO selection was based on local practice; ABO-identical products were generally selected when possible. PLT ABO matching categories were defined as follows:

- ABO identical—PLT donor and recipient have the same ABO red blood cell (RBC) antigens and plasma antibodies;
- ABO minor mismatch—donor's plasma ABO antibodies are incompatible with recipient's RBC ABO antigens (e.g., O PLT donor, A recipient);
- ABO major mismatch—donor's RBC ABO antigens are incompatible with recipient's plasma ABO antibodies (e.g., A PLT donor, O recipient).

Patients were continued on study until 30 days after the first PLT transfusion; until they had a 10-day period without a PLT transfusion; or until hospital discharge, death, or withdrawal from the study—whichever came first.

Adverse events

Information was collected prospectively on all serious adverse events that occurred while patients were on study and on specific TRAEs. TRAEs for which data were collected included allergic or hypersensitivity reaction, sinus bradycardia, sinus tachycardia, hypertension, hypotension, dyspnea, hypoxia, wheezing, cough, hemolysis, rigors or chills, fever, and infection. Grading of TRAEs was based on the Common Terminology Criteria for Adverse Events, Version 3.0[4] (see Table S1, available as supporting information in the online version of this paper). Multiple

TRAEs, with the same or different Common Terminology Criteria for Adverse Events grades, could be reported for the same transfusion. TRAEs were to be reported if they occurred during or within 4 hours after each transfusion, whether or not the clinical or transfusion service staff considered the event to be caused by the transfusion. No data were collected regarding premedication.

Statistical analysis

PLT transfusions were excluded from the analysis of TRAEs if they had one or more of the following characteristics:

- Had missing data on TRAEs (n = 4);
- Included both apheresis and WBD PLTs in the same transfusion (n = 49);
- Included any unit with missing data on ABO matching status or units with different ABO matching statuses in the same transfusion (n = 259);
- Included any units stored 6 or 7 days before transfusion, as this storage duration was extremely rare (n = 33);
- Included any units with missing data on storage duration or any units from different storage duration categories (0-2, 3, 4, or 5 days; n = 1298);
- Included any volume-reduced units (n = 593);
- Were given to any of the 41 PLADO subjects who received any HLA-selected units (n = 836, of which 314 included HLA-selected units);
- Had a TRAE period (start of transfusion to 4 hr posttransfusion) overlapping the TRAE period of any other PLT, granulocyte, or RBC transfusion (n = 2037).

Some transfusions had more than one reason for exclusion.

Analyses were carried out for three composite outcomes: any TRAE versus none, any TRAE of Grade 2 or higher versus no TRAE of Grade 2 or higher, and any TRAE of Grade 3 or higher versus no TRAE of Grade 3 or higher. Analyses were also carried out for each specific type of TRAE that occurred in at least 50 (1%) of the transfusions included in the analysis.

For each of these outcomes, a multipredictor model was fit using a generalized linear model.[5] The model included randomized dose group; PLT source; ABO matching status; storage duration (0-2, 3, 4, or 5 days); transfusion number (1st, 2nd, 3rd, 4th, 5th, 6th-10th, or later PLT transfusion while on study); stratum (autologous or syngeneic SCT, allogeneic SCT, chemotherapy for either solid tumor or hematologic malignancy); age group (0-17, 18-64, 65 or more years); and sex, plus an interaction term between dose and source, and also took into account the possible correlation of outcomes between different transfusions given to the same subject. If the interaction p value was greater than 0.05 the interaction term was dropped from the model.

Some TRAEs may be related to the number of donors contributing to the transfusion. Other TRAEs may be related to the total volume of the transfusion per m^2 BSA, the overall infusion rate per m^2 BSA for the entire transfusion episode, or the mean transfused volume per donor. Generalized linear models were used to compare these characteristics between randomized dose groups, taking into account within-person correlation. Additional generalized linear models were fit for each TRAE outcome to determine if the relationship between PLT dose and the TRAE outcome was due to differences in either number of donors or overall infusion rate. Because these were hypothesis-generating, exploratory analyses, no adjustment was made for the number of comparisons performed.

RESULTS

There were 8158 PLT transfusions administered to the 1231 patients who received at least one PLT transfusion but no HLA-selected PLTs. After exclusions for missing data or other reasons (see Materials and Methods), 5034 PLT transfusions to 1102 patients were included in the TRAE analysis. Characteristics of these transfusions are shown in Table 1.

As expected, the total volume of each transfusion per m^2 BSA differed by randomized dose group (median 79 mL/m^2 for transfusions given to patients in the LD group, 147 mL/m^2 in the MD group, and 269 mL/m^2 in the HD group; $p < 0.0001$). For a "usual size" patient of 1.7 m^2 BSA, these median volumes correspond to 134 mL per transfusion for LD, 250 mL for MD, and 457 mL for HD. The transfusion rate for the entire transfusion episode, in mL/min/m^2 BSA, also differed by randomized dose group, with the rate in the LD group significantly lower than rates in the other two groups (medians of 2.4, 3.0, and 3.6 for the LD, MD, and HD groups, respectively; $p < 0.001$ for the three-group comparison).

For apheresis PLT transfusions, 97% of transfusions in the LD and MD groups were single apheresis units, while only 43% of HD transfusions were single units. The median of the average volume transfused per individual unit was 141 mL for LD, 252 mL for MD, and 259 mL for HD PLTs. For WBD transfusions, the median number of individual donors per transfusion episode was three for LD, five for MD, and 10 for HD, and the median transfused volume per individual donor was 52 mL in all three groups.

Frequency of TRAEs

There were 310 transfusions (6.2%) associated with a maximum TRAE grade of 1, 150 transfusions (3.0%) with a

TABLE 1. Individual characteristics of the PLT transfusions

PLT or patient characteristic	Number (%)
Randomized treatment group	
LD	2267 (45)
MD	1668 (33)
HD	1099 (22)
PLT source	
Apheresis	3700 (74)
WBD	1334 (26)
PLT storage duration (days)	
0-2	406 (8)
3	1119 (22)
4	1730 (34)
5	1779 (35)
ABO matching status	
Identical	3213 (64)
Major mismatch	1412 (28)
Minor mismatch	409 (8)
Transfusion number	
1st	822 (16)
2nd	680 (14)
3rd	565 (11)
4th	438 (9)
5th	340 (7)
6th-10th	1027 (20)
11th or later	1162 (23)
Recipient sex	
Male	3109 (62)
Female	1925 (38)
Recipient age group (years)	
0-17	1210 (24)
18-64	3351 (67)
65+	473 (9)
Recipient treatment category	
Allogeneic SCT	2639 (52)
Autologous or syngeneic SCT	1100 (22)
Chemotherapy without SCT	1295 (26)

maximum grade of 2, and 41 transfusions (0.8%) with a maximum grade of 3. No transfusions in the analysis data set had a Grade 4 TRAE. The number and percentage of PLT transfusions associated with each specific type of TRAE are shown in Fig. 1. The most common TRAEs were fever (occurring in 6.6% of transfusions), followed by allergic or hypersensitivity reaction (1.9%), sinus tachycardia (1.8%), and rigors or chills (1.1%).

Relationships between PLT product and recipient characteristics and the occurrence of any TRAE during or within 4 hours after transfusion were evaluated in a multipredictor model (Fig. 2). PLT dose assignment (low, medium, or high) was a significant predictor of whether any TRAE was associated with the transfusion ($p = 0.02$ for the three-group comparison). LD and MD transfusions had similar risk, but HD transfusions were associated with a higher risk of a TRAE. PLT source, PLT storage duration, and ABO matching status were not significantly related to the risk of any TRAE occurring. The risk of a TRAE tended to decline with later transfusions ($p = 0.02$ for the seven-group comparison), and the comparison with initial PLT transfusions reached significance for the categories of 6th to 10th transfusions and 11th and later transfusions. This trend was not due to patients who experienced any TRAE receiving fewer PLT transfusions than patients without TRAEs. The number of PLT transfusions was higher among patients with any TRAE than in patients with none (median of 7 transfusions vs. 4; $p < 0.0001$). Autologous SCT recipients were at lowest risk and chemotherapy patients at highest risk of a TRAE occurring, but this did not reach significance ($p = 0.06$ for the three-group comparison).

Figure 3 shows the multipredictor model for the composite outcome of whether at least one TRAE of Grade 2 or higher occurred during or within 4 hours after the transfusion. Transfusions in the LD group were least likely to have a TRAE Grade 2 or higher, whereas transfusions in the HD group were most likely to have this outcome. However, the overall comparison of the three dose groups was not significant ($p = 0.17$). PLT source, storage duration, and ABO matching were not significantly associated with Grade 2 or higher TRAEs. Risk of a TRAE Grade 2 or higher was generally lower for transfusions after the first, although the overall comparison was not significant ($p = 0.15$). Recipient sex, age group, and treatment category were not significantly associated with Grade 2 or higher TRAEs. None of the product or recipient variables in the multipredictor model was significantly associated with occurrence of a Grade 3 or higher TRAE (data not shown).

Febrile TRAEs

Figure 4 shows the multipredictor model for the most common TRAE, fever. PLT dose was a significant predictor of fever, with transfusions in the HD group having a significantly greater risk of fever than transfusions in the MD group. ABO matching status was also a significant predictor, with minor mismatches associated with lower risk.

Allergic TRAEs

Figure 5 shows the multipredictor model for allergic or hypersensitivity TRAEs. There was a significant interaction between PLT dose and PLT source ($p = 0.04$). Among transfusions of apheresis PLTs, LD transfusions had the lowest risk, and MD transfusions had the greatest risk. Among transfusions of WBD PLTs, the MD group had the lowest risk, and the HD group had significantly higher risk than the MD group. The risk of allergic or hypersensitivity TRAE of a MD WBD PLT transfusion was significantly lower than that of a MD apheresis PLT transfusion (odds ratio [OR], 0.19; 95% confidence interval [CI], 0.05-0.76; $p = 0.02$). The risk was also lower for LD WBD PLT transfusions versus LD apheresis PLT transfusions, although this was not significant (OR, 0.59; 95% CI, 0.22-1.59; $p = 0.30$). The observed risk was higher for HD WBD PLT transfusions versus HD apheresis PLT transfusions, but

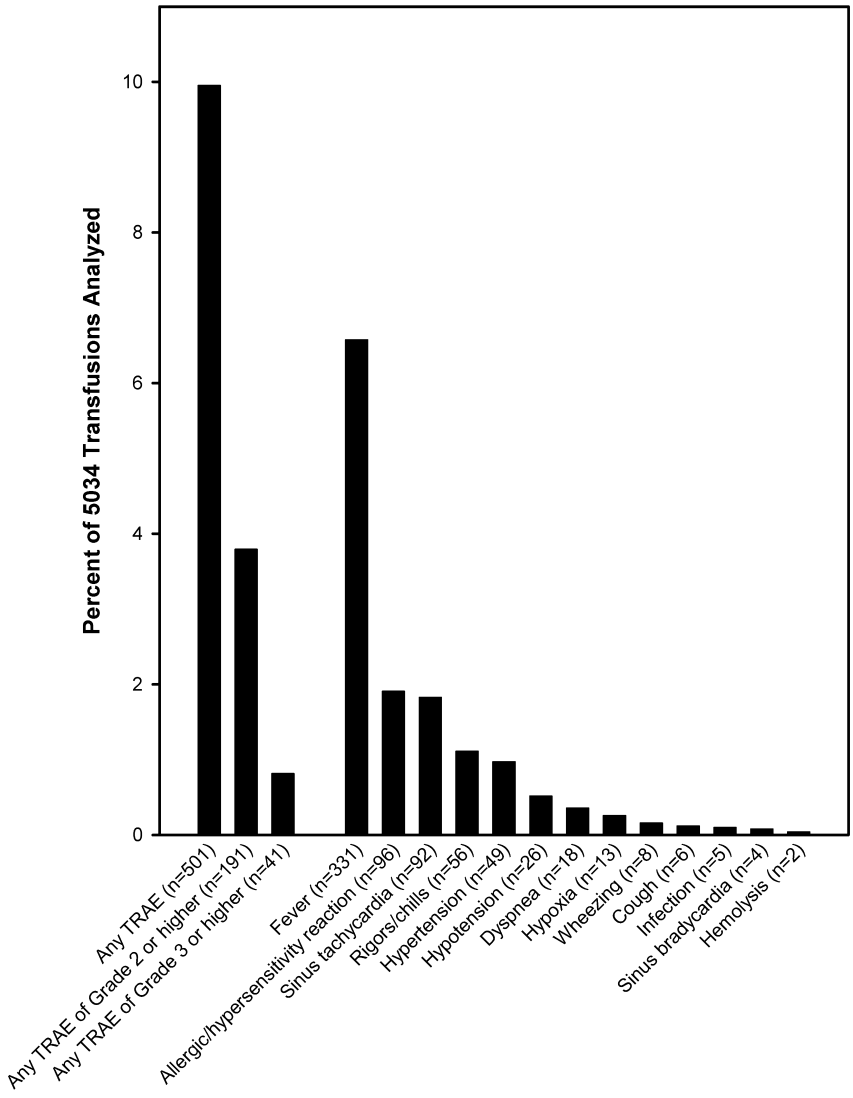

Fig. 1. Frequency of TRAEs. Although seven PLT transfusions in the PLADO study were associated with a Grade 4 TRAE, all seven met one or more of the exclusion criteria for the TRAE analysis.

this also was not significant (OR, 1.94; 95% CI, 0.78-4.82; p = 0.15). The risk of an allergic or hypersensitivity reaction tended to decrease with subsequent transfusions (seven-group p < 0.001; Fig. 5). This trend was not due to patients who experienced any allergic or hypersensitivity reaction receiving fewer PLT transfusions than patients who did not experience such a reaction. The number of transfusions was similar among patients with any allergic or hypersensitivity event and those with no such event (median of 5 vs. 5; p = 0.20). Children ages 0 to 17 years were much less likely than adults to have allergic TRAEs (OR, 0.20; 95% CI, 0.08-0.51; p = 0.001).

Other TRAEs

Sinus tachycardia was the third most common TRAE reported in the PLADO study, but it was not usually observed in isolation. Among the 92 transfusions with sinus tachycardia, one or more additional TRAEs were reported in 80 (87.0%). Fever occurred in 74 (80.4%) cases of transfusion-related sinus tachycardia. Other TRAEs often associated with sinus tachycardia included allergic or hypersensitivity reactions (8.7%), rigors or chills (8.7%), dyspnea (6.5%), hypertension (6.5%), hypoxia (6.5%), and hypotension (5.4%). Sinus tachycardia was not significantly associated with any PLT unit characteristics. However, children aged 0 to 17 years were at much higher risk of sinus tachycardia than adults (OR, 5.29; 95% CI, 2.86-9.76; three-group p = 0.001).

In the multipredictor model for chills or rigors, the risk appeared to differ between randomized dose groups (OR for the LD vs. MD group, 0.66; 95% CI, 0.32-1.36; OR for HD vs. MD, 1.95; 95% CI, 0.98-3.88; three-group p = 0.03). Children aged 0 to 17 years were at lower risk than adults for chills or rigors (OR compared to 18- to 64-year group, 0.13; 95% CI, 0.03-0.50; three-group p < 0.001).

Other than those noted above, no other significant associations between PLT unit or recipient characteristics and TRAEs were identified in the multipredictor models. When number of donors was added to each of the models, it was at least borderline significant for any TRAE (OR for each additional donor, 1.17; p < 0.001), Grade 2 or higher TRAE (OR, 1.15; p = 0.07), and fever (OR, 1.14; p = 0.01). For all three outcomes, the ORs for the dose effects were closer to 1.00 after adjusting for number of donors. For all composite and individual TRAE outcomes analyzed, infusion rate was not significant when added to the multipredictor model, nor did adding this covariate have a major effect on the relationship between transfusion dose and TRAE outcomes.

DISCUSSION

In this analysis, we assessed whether various characteristics of PLT products and recipients were associated with the risk of TRAEs. PLT dose per transfusion was the most important PLT unit characteristic associated with TRAEs in the PLADO study. PLT dose was a significant predictor of any TRAE versus no TRAE and of fever and chills or

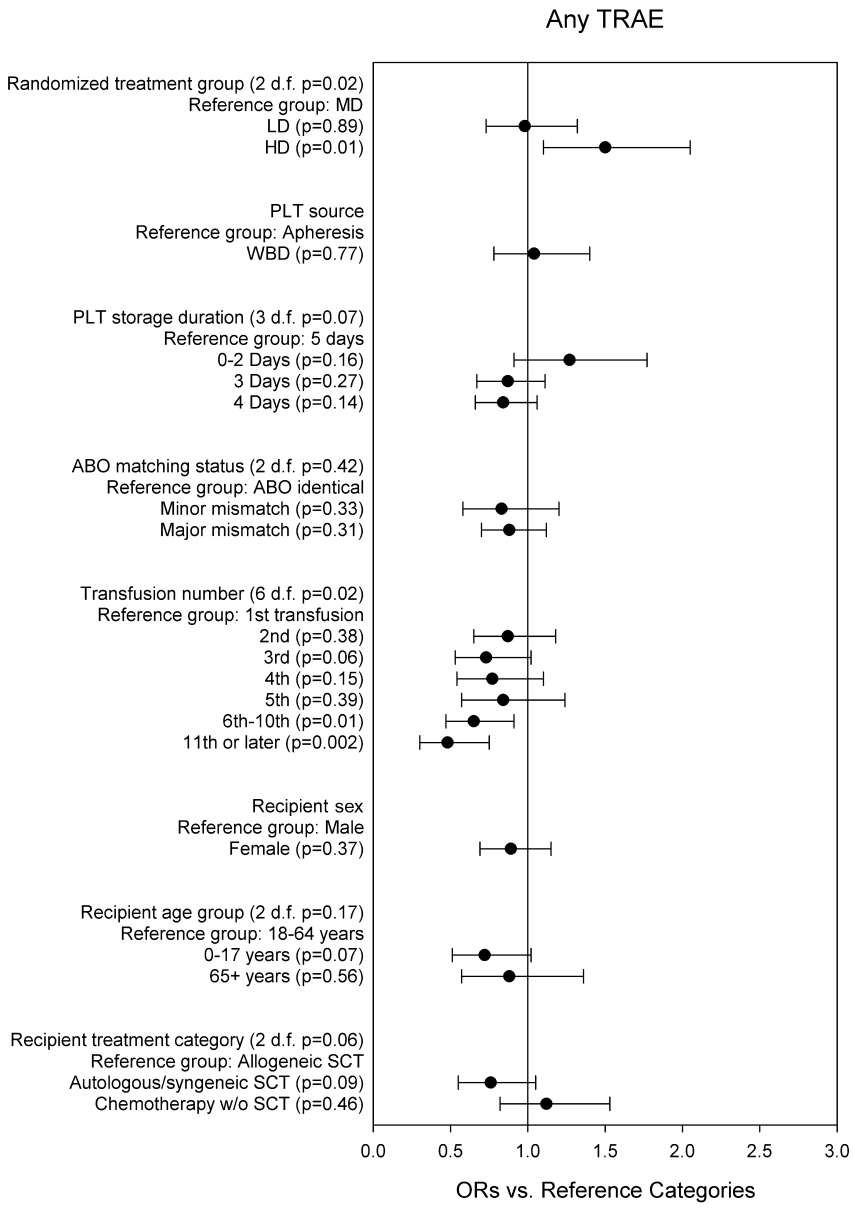

Fig. 2. Multipredictor logistic regression model for any TRAE versus no TRAE. The ORs are adjusted for all other variables in the model and for within-person correlation.

rigors. Although not reaching significance, increasing dose was also associated with increased risk for TRAEs of Grade 2 or higher. An increase in the number of donors per transfusion seems to explain at least some of the association between increased dose and increased risk. For any TRAE, Grade 2 or higher TRAE, and fever, the number of donors had a significant or borderline significant relationship to the outcome, and adding this variable to the model reduced the OR for HD versus MD. Some of the increased risk of HD PLTs may be related to the increased volume of plasma infused per transfusion. In a classic study by Heddle and colleagues[6] reported in 1994, plasma and cellular components of nonleukoreduced pooled PLT concentrates were transfused separately and in random order to recipients with thrombocytopenia. Most of the febrile nonhemolytic reactions followed transfusion of the plasma fraction, and a strong correlation was seen between the reactions and plasma concentrations of interleukin-1β and -6.

There was some indication that dose was also related to allergic or hypersensitivity reactions, although the pattern of results varied depending on whether the units were apheresis or WBD. This analysis did not provide clear data on the question of whether allergic reactions are more likely to occur with apheresis PLTs versus WBD PLTs.[7] LD and MD apheresis PLTs were more likely to be associated with allergic or hypersensitivity TRAEs than WBD PLTs in the respective dose groups. In contrast, HD apheresis PLTs were associated with lower allergic or hypersensitivity TRAE risk than HD WBD PLTs.

The incidence of any TRAE versus none tended to be higher for the initial transfusion to a given patient and decreased with later transfusions. This relationship appeared to be primarily driven by the association between transfusion number and allergic or hypersensitivity TRAEs. It is possible that this pattern is due to an increased use of pretransfusion medication among patients with reactions to a previous transfusion. Pretransfusion medication strategies were not specified in the PLADO protocol, and data were not collected on whether, or which, pretransfusion medications were administered, so this hypothesis cannot be addressed directly. However, most studies performed to date have failed to demonstrate that pretransfusion medication, typically with acetaminophen and diphenhydramine, is effective in preventing febrile or allergic transfusion reactions.[8-11] In addition, the risk of fevers stayed fairly constant as the number of PLT transfusions increased, making the pretransfusion medication hypothesis less likely, unless pretransfusion medication to prevent allergic reactions is more efficacious than pretransfusion medication to prevent fever. A second possibility is that recurrent exposure to donor PLTs caused recipients to become less likely to experience allergic reactions.[12] Experiments performed in volunteers during the

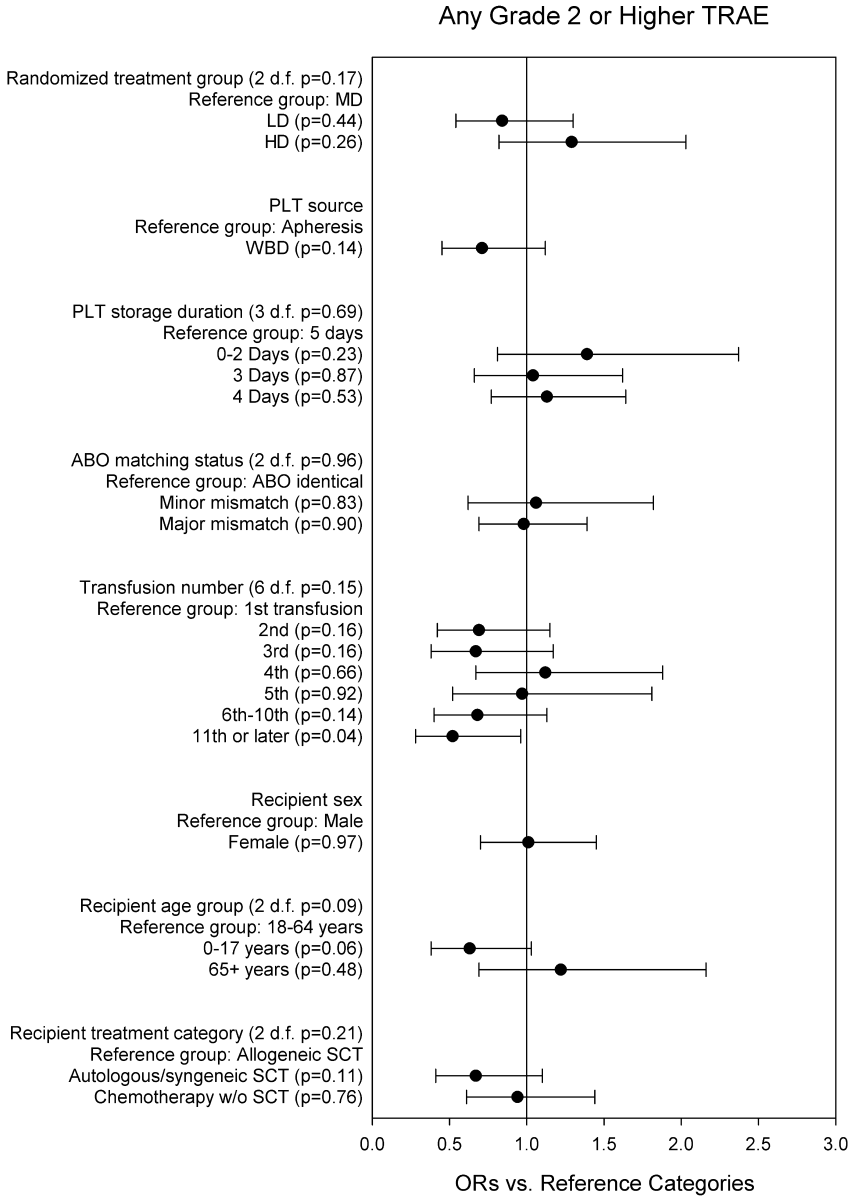

Fig. 3. Multipredictor logistic regression model for any TRAE of Grade 2 or higher versus no TRAE of Grade 2 or higher. The ORs are adjusted for all other variables in the model and for within-person correlation.

1940s did in fact show a "desensitization" effect on repeat exposure to reconstituted donor serum.[13] These two hypotheses are not mutually exclusive.

A minority of the PLT transfusions in PLADO were ABO mismatched, either major (28%) or minor (8%). ABO-identical PLT transfusions are well established to provide a better increment than ABO major-mismatched PLT transfusions.[14,15] However, the effect of PLT ABO matching on transfusion reaction risks has been less clear.[16] In this analysis, ABO matching status was not significantly associated with any of the TRAE outcomes except fever. Minor ABO-mismatched PLTs were associated with a lower risk of fever; we speculate that this was a chance association.

Some patient characteristics were associated with TRAE outcomes. Compared to allogeneic hematopoietic SCT recipients, autologous hematopoietic SCT recipients were somewhat less likely to have any TRAE, while patients receiving chemotherapy were slightly more likely to have any TRAE. Sinus tachycardia was more common in children than adults. However, allergic reactions and rigors or chills were much less common in children than adults. The published data are conflicting regarding the relative rates of allergic transfusion reactions in children versus adults.[17,18] We speculate that children may be less likely than adults to clearly report symptoms of allergic reactions or other types of reactions.

This study had a number of important limitations. While all PLADO data were collected prospectively, the analysis of TRAEs was a post hoc secondary analysis. Only the dose of prophylactic PLT transfusions was randomized in PLADO, and the results obtained for characteristics other than PLT dose may have been affected by confounding factors that were not included in the models. The primary outcome of the PLADO study was clinical bleeding, and PLADO was not specifically powered to examine TRAE endpoints, most of which were fairly rare. Some or all of the significant findings may be due to chance. A large number of comparisons were performed, and because this was an exploratory analysis statistical adjustments for multiple comparisons were not made. All patients in the PLADO study were hematology-oncology patients; therefore, the results obtained may not be applicable to other patient groups. Presumably, not all of the TRAEs reported in this article represented true transfusion reactions. For example, in the hematologic malignancy patient population studied, intercurrent infections occur frequently. Many of the fevers classified as TRAEs were probably caused by underlying disease rather than transfused leukoreduced PLTs. Data were not collected on whether the caregivers considered each TRAE to be a true transfusion reaction or whether there were other more plausible explanations for the event.

Considerable uncertainty exists around the true incidence of adverse reactions caused by PLT transfusions.

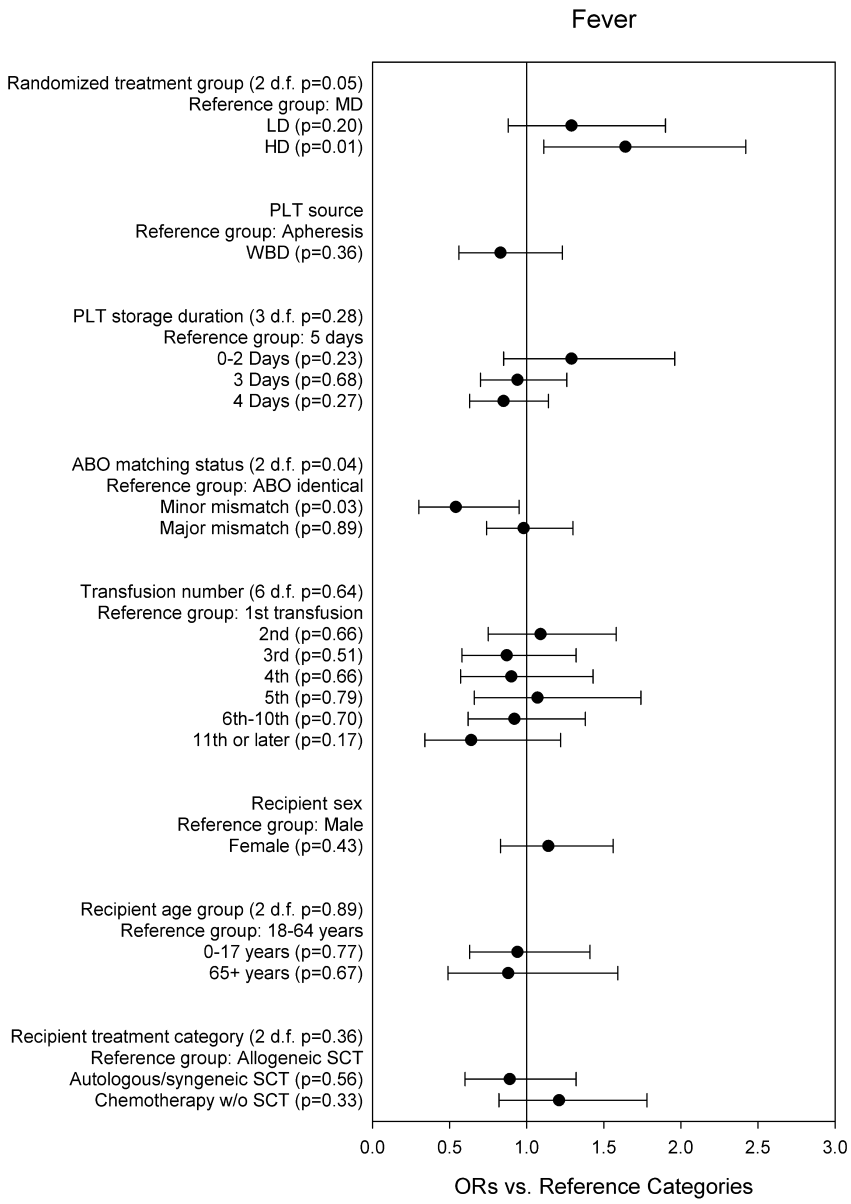

Fig. 4. Multipredictor logistic regression model for any fever TRAE versus no fever TRAE. The ORs are adjusted for all other variables in the model and for within-person correlation.

Febrile nonhemolytic transfusion reactions, for example, have been reported to occur with anywhere from 0.09% to more than 27% of PLT transfusions, an extraordinarily wide range.[8] Many factors potentially contribute to the variability in published adverse event rates, including prospective versus retrospective data collection, disparities in reporting, variation in the PLT products transfused (WBD vs. apheresis, leukoreduced vs. nonleukoreduced, etc.), and differences among the recipient populations studied. Rigorously conducted prospective trials in transfusion medicine provide the potential advantage of capturing more detailed and consistent reporting of TRAEs than is commonly done as part of standard care. Additionally, clinical trial data may allow comparisons to be adjusted for more potentially confounding variables than data from retrospective observational studies. For the current analysis, we were able to leverage the large volume of data systematically collected during the PLADO trial to examine the effects of both product and recipient factors on the risks of various adverse consequences of PLT transfusion. However, even large clinical trials such as PLADO include fewer transfusions than many hemovigilance studies, resulting in lower statistical power, especially for less common outcomes.

The PLADO study showed that PLT dose per transfusion had no impact on whether patients experienced any Grade 2 or higher bleeding or on the time that it took for Grade 2 or higher bleeding to develop. Additional post hoc analyses of PLADO data demonstrated that PLT source, storage duration, and ABO matching status were not significantly related to clinical bleeding outcomes. These factors were, however, significantly associated with post-transfusion PLT count increments in transfusion recipients. In this secondary analysis, we determined that LD PLT transfusions carried a lower overall TRAE risk than HD PLT transfusions. The TRAE risk of LD transfusions was similar to, and possibly lower than, that of MD PLT transfusions, which approximate current standard care (1 apheresis PLT unit or a pool of 4-6 WBD units for a typical adult dose). We believe that this analysis further supports the concept that LD PLTs are a safe and effective strategy for PLT prophylaxis.

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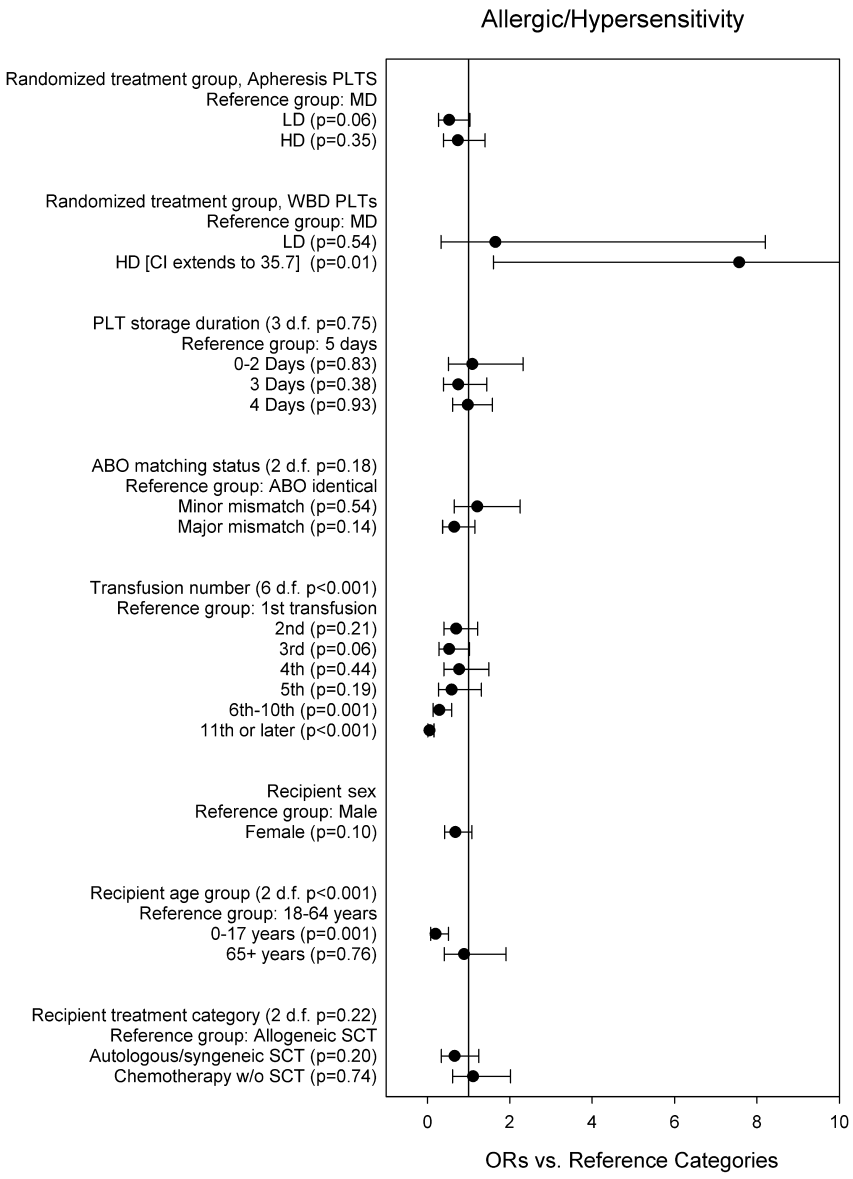

Fig. 5. Multipredictor logistic regression model for any allergic or hypersensitivity TRAE versus no allergic or hypersensitivity TRAE. The ORs are adjusted for all other variables in the model and for within-person correlation.

CONFLICT OF INTEREST

DJT is on the medical advisory board for Fenwal Fresenius Kabi. PN is a consultant for TerumoBCT, Lakewood, CO. The remaining authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's Web site:

Table S1. Grading criteria used for transfusion-related adverse events in PLADO, based on Common Toxicity Criteria for Adverse Events v3.0. All events on this list were to be reported if they occurred during or within 4 hours after the end of a transfusion, whether or not the event was judged to be caused by the transfusion.