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TRANSFUSION MEDICINE

The effect of variation in donor platelet function on transfusion outcome: a semirandomized controlled trial

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Key Points

- There is variation in platelet function between normal individuals, and this function is consistent within the same individual over time.
- The data from this study suggest that variation in donor platelet function does not affect the outcome of prophylactic transfusion.

The effect of variation in platelet function in platelet donors on patient outcome following platelet transfusion is unknown. This trial assessed the hypothesis that platelets collected from donors with highly responsive platelets to agonists in vitro assessed by flow cytometry (high-responder donors) are cleared more quickly from the circulation than those from low-responder donors, resulting in lower platelet count increments following transfusion. This parallel group, semirandomized double-blinded trial was conducted in a single center in the United Kingdom. Eligible patients were those 16 or older with thrombocytopenia secondary to bone marrow failure, requiring prophylactic platelet transfusion. Patients were randomly assigned to receive a platelet donation from a high- or low-responder donor when both were available, or when only 1 type of platelet was available, patients received that. Participants, investigators, and those assessing outcomes were masked to group assignment. The primary end point was the platelet count increment 10 to 90 minutes following transfusion. Analysis was by intention to treat. Fifty-one patients were assigned to receive platelets from low-responder donors, and 49 from high-responder donors (47 of which were randomized and 53 nonrandomized). There was no significant difference in platelet count increment 10 to 90 minutes following transfusion in patients receiving platelets from high-responder (mean, 21.0 × 10^9/L; 95% confidence interval [CI], 4.9-37.2) or low-responder (mean, 23.3 × 10^9/L; 95% CI, 7.8-38.9) donors (mean difference, 2.3; 95% CI, −1.1 to 5.7; *P* = .18). These results support the current policy of not selecting platelet donors on the basis of platelet function for prophylactic platelet transfusion. (*Blood*. 2017;130(2):214-220)

Introduction

Most platelets are transfused prophylactically, on the basis of platelet count, to reduce the risk of bleeding in patients who have developed thrombocytopenia as a result of treatment of hematological malignancies.[1] Blood services ensure the safety and efficacy of platelets for transfusion through validation of new processes for their collection, production and storage, and compliance with regulatory standards. However, little attention has been paid to the effect of donor-related variation in the donated material on patient outcomes. This is particularly relevant to platelets collected by apheresis (derived from single donors), where platelet dysfunction in the donor will have a larger effect than those derived from a pool of 4 or more whole blood donations.

Unlike drugs that can be produced to uniform potency, the composition of platelet concentrates for the prevention or treatment of bleeding varies, mainly because of natural variation in hematological traits between donors. Platelet function is highly variable between individuals, but for a given individual, it is highly consistent over time.[2] These observations, together with those in twins,[3] suggest that platelet function is to a large extent a heritable trait. Consequently, there is great interest in how such variation may relate to an individual's risk of thrombosis or bleeding and in tailoring of pharmacological interventions to reduce this risk. We have shown that inherent variation in platelet responsiveness to agonists assessed by flow cytometry is to a large extent genetically controlled, by employing methods that assess 2 well-characterized but distinct platelet signaling pathways known to be important in platelet activation after atherosclerotic plaque rupture and that provide information on both platelet receptor activation and degranulation.[4] We have identified 24 genes that show an association between platelet responsiveness and sequence variation and demonstrated that platelet responsiveness of a donor at the extremes of the distribution of responses (high or low) is reproducible over time[4,5] and that donors with highly responsive platelets are more likely to produce a unit of platelets containing a higher level of activated platelets.[6]

Whether increased activation that occurs during storage of platelets reduces platelet survival once transfused is unclear. Data from animals models are mixed; some suggest that platelet activation is related to platelet clearance,[7] whereas others suggest that this is not the case.[8,9] In

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humans, several studies have suggested that increased platelet activation in platelet concentrates might be associated with reduced survival following infusion to healthy subjects,[10,11] whereas others have failed to observe such a relationship.[12]

There is increasing evidence to suggest that phenotypic and proteomic changes that occur during the storage of red cells and platelets for transfusion may in part be determined by the genotype of the donor.[13-15] These observations and others have led to an increased international focus on the role of the donor in the quality of red cells and platelets for transfusion. Reduced costs and ease of genotyping now make large-scale testing of donors a reality. It is therefore important to understand whether genetic variation in platelet function at the point of donation and/or on subsequent storage translates into clinically relevant outcomes for recipients of platelets. This is the first study in the literature to examine this question.

We conducted a trial in patients receiving platelets for prophylaxis to assess whether differences in platelet function in the donor population affect the clinical outcome from platelet transfusion. To maximize the likelihood of observing a difference between groups, we selected donors with platelet responsiveness at the extreme ends of the distribution (high or low responders). We hypothesized that platelets derived from high-responder donors would be cleared more rapidly from the circulation than those from low-responder donors, leading to lower platelet count increments following transfusion and potentially a shortening of the time until the next platelet transfusion was required.

Methods

Study design

We conducted a parallel-group, double-blinded, semirandomized trial at a single center in the United Kingdom, the PROmPT (Platelet Responsiveness and Outcome from Platelet Transfusion) trial. Patients were randomized to receive a single platelet transfusion from either a high- or low-responder donor. Because it was possible that platelets from high- or low-responder donors may not differ from each other, but that either might differ from those from donors of average responsiveness, we concurrently enrolled a group of 30 patients that received platelets from unselected donors for comparison (referred to as unselected units). Participants, treating clinicians, and those assessing outcomes and analyzing data were blinded to treatment group throughout. Randomization was performed using unstratified permuted blocks via an online randomization service (http://www.sealedenvelope.com) by randomization coordinators who were not part of the trial personnel involved in the enrollment, treatment, or measurement of outcomes. The protocol included a prespecified interim analysis after 20 patients presented for randomization, as we predicted that insufficient platelet availability might result in an unacceptably low percentage of enrolled patients being randomized. The study protocol specified that in such circumstances an alternative treatment allocation procedure would be followed, resulting in a semirandomized study: when donor platelet units from both high and low responders were available, patients would be randomized to receive either, but if only 1 type of platelet unit was available (ie, from either a high or low responder), the patient would receive that unit (nonrandomized). Although the allocation was not randomized in this circumstance, blinding was maintained. If neither was available, then patients received a suitable platelet unit from an unselected donor. The full study protocol is publically available.[16]

Participants

Donors. We previously established a cohort of 506 donors whose platelets were tested by flow cytometry for responsiveness to 2 agonists (collagen-related peptide-XL or adenosine diphosphate) each with 2 measures of response (fibrinogen binding or P-selectin expression) resulting in 4 end points.[4] To provide sufficient donors for this study, we increased this cohort to 956 by testing an additional 450 donors using the same methods. To determine the platelet responsiveness phenotype, the percentage positive (PP) platelets for each of the 4 end points was transformed to the logit scale, that is, $\log[PP/(100 - PP)]$, and then a multiple linear regression model was applied with the date of sample testing as a continuous predictor. To combine the data into 1 overall measure of platelet response and thus assign the donor to a high or low category, the data from each of the 4 end points were transformed so that the data from each output occupied the same range and distribution as described previously.[4] The standardized residual from the regression model was used to rank how far an individual donor deviated from the average response. High responders were defined as those with the highest minimum response, and low responders as those with the lowest maximum of all 4 end points. Those donors with the most reproducible responses in the upper and lower 10% of the distribution were selected to form a panel of donors for the study (26 high-responder and 19 low-responder donors). An example of donor selection can be found in the supplemental Data (available on the *Blood* Web site).

The testing of donors was approved by the Huntingdon Research Ethics Committee (Reference 05/Q0104/27).

Patients. Eligible patients, aged 16 years or older, were stable hematology patients requiring platelets for prophylactic transfusion. Both inpatients and outpatients were recruited, and diagnoses included acute leukemia, bone marrow failure, and both autologous and allogenic transplant. Exclusion criteria included patients with inherited or acquired coagulation or platelet function disorders, with current acute promyelocytic leukemia or other active malignancy in past 5 years (other than the current primary diagnosis), with previously documented World Health Organization (WHO) grade 4 bleeding, with palpable splenomegaly, who were pregnant or lactating, with immunological refractoriness to platelet transfusion, or who required HLA- or human platelet antigen–matched platelets. Patients were temporarily excluded from the trial for factors such as fever that might influence the primary and secondary end points measured (see supplemental Data). Once resolved, patients with temporary exclusion criteria were eligible for inclusion. Patients were eligible to receive a single transfusion from both an unselected donor and either 1 high- or low-responder donor in the course of their treatment, but only once the follow-up period from their previous trial transfusion was complete (5 days or until their next platelet transfusion).

Approval for the study was granted from the Hertfordshire Research Ethics Committee (Reference 11/EE/0227).

Procedures

Donors for the study fulfilled all requirements for platelet donation according to national guidelines.[17] Leukocyte-depleted platelets were collected by apheresis using a single type of collection device for the entire study duration (Trima Accel; Terumo BCT, Lakewood, CO) and stored in plasma for up to 5 days from donation. Patients that were likely to become thrombocytopenic and require a prophylactic platelet transfusion were enrolled by their clinical care team. The decision to transfuse was made by the clinician caring for the patient, usually when the platelet count fell below 10×10^9/L according to local and national guidelines. Patients received a single unit of platelets and were followed up for 5 days or until their next platelet transfusion. Platelets were matched for ABO and RhD blood group according to local guidelines. The threshold for red cell transfusion in the absence of bleeding was 90 g/L hemoglobin. Blood samples were taken on the day of transfusion and 10 to 90 minutes and 12 to 36 hours after transfusion. A full blood count was made on samples anticoagulated with EDTA using a hematology analyzer to measure platelet count (LH750; Beckman Coulter, High Wycombe, United Kingdom). Bleeding symptoms were recorded on the day of transfusion and daily thereafter by the clinical team and by validated patient self-assessment.[18] Clinician and patient self-assessment were made for days when patients were in hospital, but patient self-assessment only for periods of follow-up when patients were at home. Bleeding was graded according to a modified WHO system by the use of a computer-generated algorithm. In this the most commonly used method of assessing bleeding in platelet transfusion trials, bleeding is categorized as grade 1 (mild), grade 2 (moderate, not usually requiring red cell transfusion), grade 3 (severe, requiring red cell transfusion), and grade 4 (debilitating or life threatening). In accordance with a recent trial of platelet transfusion that required assessment of bleeding,[19] 2 types of grade 1 bleeding (spreading or generalized petechiae or a nose bleed lasting >30 minutes) were classified as grade 2 for this study because these may be considered clinically significant in patients with thrombocytopenia and regarded by many treating clinicians as a trigger for platelet transfusion.

Outcomes

The primary outcome was the platelet count increment 1 hour (10-90 minutes) following transfusion (ie, the difference between platelet count before and after transfusion). Secondary outcomes were the platelet count increment at 24 hours (12-36 hours); the corrected count increment (CCI) at 1 hour (10-90 minutes) and 24 hours (12-36 hours); number of patients with at least 1 WHO bleeding event grade 2, 3, or 4 within the follow-up period; number of days with WHO bleeding events grade 2, 3, or 4 within the follow-up period; number of red cell transfusions within the follow-up period; and time to next platelet transfusion. The CCI was defined as (count increment $\times$ body surface area [BSA])/ platelet dose ($\times 10^{11}$). Bleeding assessed by study clinician and patient self-assessment were considered as separate outcomes. Data on adverse events were collected according to standard definitions used in the UK Serious Hazards of Transfusion Haemovigilance scheme. Events that were judged to be expected and as a result of the patient's underlying diagnosis were not reported as serious adverse events (SAEs) but were logged as adverse events. The rationale for choice of end points can be found in the full study protocol.[16]

Statistical analysis

The required sample size was calculated based on the difference in the platelet count increment (primary outcome) following transfusion between patients receiving platelets from high- or low-responder donors. Interim data from another clinical study of platelets ongoing in our organization at the time and since reported for the same measure[20] gave a standard deviation of 11.5×10^9/L (at 12-36 hours, from 65 patients and 95 transfusions). Based on 80% power, a 5% significance level, and a presumed 10% dropout rate, 100 patients (50 in each group) would be required to detect a mean difference of 7×10^9/L between the 2 groups.

A secondary set of analyses included patients who received units from unselected donors, in order to assess whether units from high- or low-responder donors differed from those from donors not at the extremes of the distribution. Recruiting 30 patients who received platelets from unselected donors allowed calculation of a 95% confidence interval (CI) for the difference in platelet increments between a treatment group and the unselected group to within ± 2.5 (ie, the width of the CI will be 5). As some of the patients that received a transfusion from an unselected donor also received a transfusion from a high- or low-responder donor, this also increased the precision of estimates.

All analyses were by intention to treat, and all patients allocated to receive a trial unit were included in the analysis, regardless of whether they were randomized to receive that unit or not, except for 2 patients in the unselected group who received a pooled platelet concentrate rather than apheresis and were excluded from analysis. Analyses were 2-sided, and the significance level was 5%. Platelet count increments at 1 and 24 hours were analyzed using a mixed-effects linear regression model with a treatment-time interaction. In order to increase power, the model was adjusted for BSA, platelet dose, and age of platelet unit, factors known to affect these outcomes. All patients with an observed platelet count increment at either 1 or 24 hours were included in the analysis. Further details of the regression models used can be found in the supplemental Data, and methods for dealing with missing data are given in the study Statistical Analysis Plan.[21]

An independent data monitoring committee reviewed patient safety and the results of the interim data analysis. The study was adopted by the National Cancer Research Network and included in the UK National Institute for Health Research (NIHR) Clinical Research Network Portfolio. Because of a change in trial managers in the run-up to trial commencement, and the reminders to register the trial being sent to an obsolete e-mail account, the trial was registered on the International Standard Randomised Controlled Trial Number (ISRCTN) database (ISRCTN56366401) about halfway through recruitment (first patient enrolled October 2011, trial registered November 2012, and last patient enrolled December 2013).

Results

The interim analysis took place after 21 patients had presented for randomization, of which only 9 had been successfully randomized, predominantly because of insufficient supply of trial units. Therefore, as prespecified in the protocol, the study became semirandomized at that point.

Of 428 patients screened, 252 consented to be part of the study (Figure 1). Of the 252 patients who consented, 137 were not allocated to receive a transfusion as there was either no suitable platelet unit available or the patient had a temporary exclusion criterion. One hundred patients were allocated to receive a trial unit: 49 from a high-responder donor (23 randomized, 26 nonrandomized) and 51 from a low-responder donor (24 randomized, 27 nonrandomized). One patient due to receive platelets from a donor in the low-responder group withdrew consent prior to transfusion. Therefore, 49/49 patients in the high-responder group and 50/51 in the low-responder group received their allocated trial unit. Thirty patients consented and were assigned to receive a transfusion from an unselected donor. Two of the 30 patients received a pooled platelet concentrate rather than apheresis and were excluded from analysis. In total, 15 patients received a transfusion from both an unselected donor and either a high- or low-responder donor.

Baseline characteristics were well matched between study groups (Table 1). Platelets for the trial were derived from 15 high-responder and 16 low-responder donors. Platelet units that were ABO identical to that of the donor were received by 96% of patients, and 98% of trial units transfused were irradiated. All RhD-negative patients received RhD-negative units.

The platelet count increment at 1 hour (the primary end point) was available for 90% of patients in the low-responder group and 100% of patients in the high-responder group. For the 24-hour platelet count increment, these values were 90% and 96% respectively. Assessment of bleeding symptoms by a clinician was made for 94% of patients in the low-responder group and 90% in the high-responder group, and by patient self-assessment for 92% and 94% of patients, respectively. Data on red cell transfusions and time to next platelet transfusion were collected on 100% of patients.

Results are shown in Tables 2 and 3. There was no significant difference between patients receiving platelets from high- or low-responder donors in either the 1-hour platelet count increment (primary end point) (low responder [23.3×10^9/L] vs high responder [21.04]; difference, 2.30; 95% CI, -1.09 to 5.69; $P = .18$) or the 24-hour platelet count increment (high responder [12.90] vs low responder [14.31×10^9/L]; difference, 1.41; 95% CI, -1.96 to 4.78; $P = .41$). There was also no significant difference between groups in CCIs at 1 or 24 hours.

There were no significant differences in any bleeding outcome between patients receiving platelets from high- or low-responder donors, including clinician-assessed bleeding scores (odds ratio, 0.78; 95% CI, 0.29-2.16; $P = .64$) and number of days with a grade 2 to 4 bleed (rate ratio, 0.70; 95% CI, 0.16 to 2.97; $P = .63$; Table 3). In addition, there was no significant difference in any of the outcomes measured between high- or low-responder groups and patients that received platelets from unselected donors (Tables 2 and 3).

There was 1 febrile transfusion reaction reported in the low-responder arm of the trial. This was initially reported as an SAE, but on further analysis did not meet criteria as the patient recovered rapidly with no increased duration of hospitalization. There were no other SAEs.

Discussion

In the first controlled trial to assess whether differences in the level of platelet responsiveness in the donor population affect clinical outcome, we have shown that the outcome from prophylactic platelet transfusion

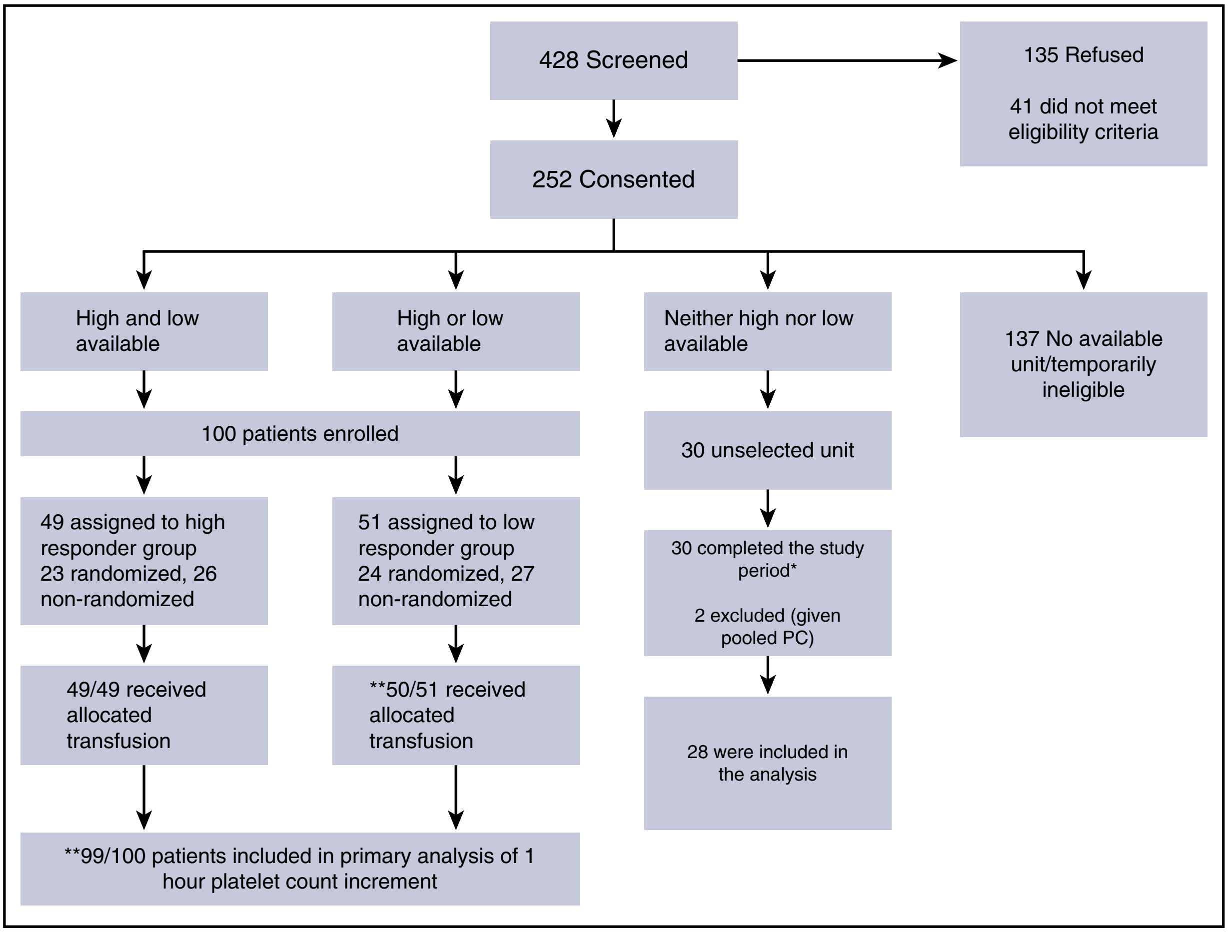

Figure 1. Study enrollment and randomization. Single asterisk indicates 15 patients also received a unit from a high- or low-responder donor. Double asterisks indicate 1 randomized patient withdrew consent prior to transfusion. PC, platelet concentrate.

in hematology patients does not differ whether the donor of the platelets has very low or highly responsive platelets to agonists in vitro.

The results from our study add to those conducted in healthy subjects and suggest that the ability of platelets to survive in the circulation following transfusion to patients is not related to how responsive the platelets of the donor are. Because the main indication to transfuse platelets is to prevent bleeding, and there is a poor correlation between bleeding risk and platelet count increments in thrombocytopenic patients, we also assessed bleeding according to the WHO grading system, the most commonly used method of assessing bleeding in platelet transfusion trials. We also collected data on the number of red cell transfusions and time to next platelet transfusion as surrogates for bleeding. There was no significant difference between groups in any of these end points. Although the study was not powered with bleeding as the primary end point, these data indicate that in addition to there being no difference in the survival of platelets following transfusion between groups, the ability of platelets to prevent bleeding was also not different. The percentage of patients experiencing grade 2 or higher bleeding symptoms was lower in this study (18% to 25%) compared with other recent prophylactic platelet trials such as the trial of prophylactic vs no prophylactic platelet transfusion (TOPPS) (43%) and dose of prophylactic platelet transfusions and prevention of hemorrhage (PLADO) (70%). We attribute this to the strict exclusion criteria in this study, especially temporary deferral for fever, and because patients were only studied for 1 platelet transfusion.

Only 2 other clinical studies have attempted to address whether differences in the functionality of platelets might influence outcome from platelet transfusion. An observational study measuring levels of P-selectin, a marker of platelet activation, in platelet concentrates suggested that lower 1-hour count increments were observed with increasing levels of platelet activation.[22] However, the study was too small (8 patients) to draw any conclusions. In another observational study, transfusions to 40 children were retrospectively categorized into 2 groups (high and low) based on the immature platelet fraction (IPF) of the platelet concentrate transfused.[23] The IPF is a parameter reported by some hematology analyzers that indicates the proportion of platelets that are reticulocytes, those platelets most recently formed.[24] Those receiving platelets from the "high" group received fewer platelet transfusions and had fewer bleeding episodes, although the method of assessing bleeding in the study is unclear. In our study, we observed a higher IPF in the whole blood of high-responder donors, but following transfusion, there was no difference in the IPF measured between patients receiving platelets from high- or low-responder donors (data not shown). This discrepancy could be because of preferential removal of subpopulations of platelets by either the apheresis device or transfusion set.

The data from our study are intriguing, indicating that differences identified by laboratory testing of measures such as platelet responsiveness in platelet donors prior to donation do not translate to differences in clinical outcome from platelet transfusion. It is therefore essential that major changes to platelet production that might affect their function undergo clinical assessment prior to introduction, rather than rely solely on laboratory data. In addition, there is insufficient evidence to recommend that platelet donors be

Table 1. Baseline characteristics of patients

	Phenotype of platelet donor		
Characteristics	**Unselected (n = 28)***	**High responder (n = 49)†**	**Low responder (n = 51)‡**
Age, mean (SD), y	52.5 (16.0)	52.2 (16.6)	49.7 (17.8)
Male, no. (%)	22 (79)	29 (59)	27 (53)
BSA, mean (SD)	1.95 (0.20)	1.91 (0.21)	1.89 (0.24)
Diagnosis, no. (%)			
Acute myeloid leukemia	10 (36)	15 (31)	18 (35)
Acute lymphoblastic leukemia	2 (7)	3 (6)	6 (12)
Chronic myeloid leukemia	0	0	0
Lymphoma	7 (25)	14 (29)	15 (29)
Myeloma	5 (18)	9 (18)	6 (12)
Other	4 (14)	8 (16)	6 (12)
Treatment plan, no. (%)			
Induction	6 (21)	8 (16)	9 (18)
Consolidation	1 (4)	2 (4)	4 (8)
Autograft	10 (36)	16 (33)	10 (20)
Allograft	6 (21)	8 (16)	12 (24)
Other	5 (18)	15 (31)	16 (31)
Pretransfusion platelet count, mean (SD), $\times 10^9$/L	8.96 (3.81)	9.73 (4.81)	10.51 (5.94)
Irradiated platelets given, no. (%)	27 (96)	48 (98)	50 (98)
Volume of platelets transfused, mean (SD), mL	176 (13.6)	175 (10.11)	174 (12.42)
Platelet dose transfused, mean (SD), $\times 10^9$	269 (49)	264 (40)	244 (30)
Platelet dose transfused per BSA, mean (SD), $\times 10^9$/m^2	140 (32)	142 (27)	130 (19)
Age of platelets, median (IQR), d	4 (4-5)	4 (3-5)	4 (3-5)
ABO fully matched, no. (%)	26 (93)	47 (96)	49 (96)
No. of donors§	N/A	15	16

Values are means with standard deviation (SD) except for age of platelets (median with interquartile range [IQR]).

N/A, not available.

*For dose transfused ($\times 10^9$ or 10^9 per BSA), n = 15.

†For dose transfused ($\times 10^9$ or 10^9 per BSA), n = 44.

‡For pretransfusion platelet count, n = 49; and for dose transfused ($\times 10^9$ or 10^9 per BSA), n = 48.

§The number of donors who have donated platelets transfused to patients. There were no significant differences between groups.

selected on the basis of platelet function. Therefore, our data support the current policy employed by blood services internationally of not assessing platelet function in apheresis donors prior to donation.

The strengths of our study include the high level of adherence to protocol and little loss to follow-up or missing data. Although ~50% of patients were not randomized, the number of transfusions from high- or low-responder donors was almost equal, the baseline characteristics of patients between groups were similar, and the blinding of the study meant that study personnel could not bias outcomes between groups. Limitations of our study include that patients received a single trial transfusion only. Data from trials of pathogen inactivated platelets have

Table 2. Primary and secondary platelet count increment outcomes

	Phenotype of platelet donor			
		High responder (n = 49)	**Low-responder platelets (n = 51)**	
Outcome	**Unselected (n = 28)**	**Difference from unselected group**	**Difference from unselected group**	**Difference from high-responder group**
Platelet increment at 1 h, mean (SE)	24.00 (1.96)	22.96 (1.54)	22.39 (1.25)	
Difference in means (95% CI)	NA	−2.20 (−6.15, 1.75)*	−0.15 (−4.31, 4.02)*	2.30 (−1.09, 5.69)†
P	NA	.28*	.95*	.18†
Platelet increment at 24 h, mean (SE)	15.61 (1.75)	14.87 (1.42)	13.74 (1.27)	
Difference in means (95% CI)	NA	−2.06 (−5.72, 1.59)*	−0.93 (−4.82, 2.96)*	1.41 (−1.96, 4.78)†
P	NA	.27*	.64*	.41†
CCI at 1 h, mean (SE)	17.13 (1.22)	16.26 (0.84)	17.29 (0.84)	
Difference in means (95% CI)	NA	−1.46 (−4.13, 1.22)‡	−0.12 (−2.84, 2.60)‡	1.36 (−0.89, 3.61)§
P	NA	.29‡	.93‡	.24§
CCI at 24 h, mean (SE)	11.01 (1.08)	10.51 (0.88)	10.40 (0.86)	
Difference in means (95% CI)	NA	−1.12 (−3.69, 1.44)‡	−1.02 (−3.54, 1.49)‡	0.13 (−2.18, 2.44)§
P	NA	.39‡	.43‡	.91§

NA, not applicable; SE, standard error.

*Taken from a linear mixed-effects model on both 1 and 24 h time points with the unselected group as reference, adjusted for BSA, the platelet dose transfused, and age of platelets transfused.

†Taken from a linear mixed-effects model on both 1 and 24 h time points with the high-responder group as reference, adjusted for BSA, the platelet dose transfused, and age of platelets transfused.

‡Taken from a linear mixed-effects model on both 1 and 24 h time points with the unselected group as reference, adjusted for age of platelets transfused.

§Taken from a linear mixed-effects model on both 1 and 24 h time points with the high-responder group as reference, adjusted for age of platelets transfused.

Table 3. Secondary bleeding outcomes

		Phenotype of platelet donor		
		High responder (n = 49)	Low responder (n = 51)	
Outcome	Unselected (n = 28)	Difference from unselected group	Difference from unselected group	Difference from high-responder group
Patients with grade 2-4 bleed: clinical assessment, no. (%)	7 (25)	10 (20)	9 (18)	
Odds ratio (95% CI)	NA	0.84 (0.28, 2.56)	0.66 (0.21, 2.03)	0.78 (0.29, 2.16)
P	NA	.76	.47	.64
Patients with grade 2-4 bleed: patient self-assessment, no. (%)	8 (29)	16 (33)	21 (41)	
Odds ratio (95% CI)	NA	1.27 (0.45, 3.53)	1.92 (0.70, 5.25)	1.51 (0.66, 3.49)
P	NA	.65	.20	.33
Days with grade 2-4 bleed: clinical assessment, median (IQR)	0 (0-1)	0 (0-0)	0 (0-0)	
Rate ratio (95% CI)	NA	0.66 (0.13, 3.41)	0.46 (0.09, 2.30)	0.70 (0.16, 2.97)
P	NA	.62	.34	.63
Days with grade 2-4 bleed: patient self-assessment, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	
Rate ratio (95% CI)	NA	0.86 (0.25, 2.98)	1.05 (0.31, 3.52)	1.26 (0.53, 3.00)
P	NA	.81	.94	.60
Red cell transfusions, median (IQR)	0 (0-1)	1 (0-1)	0 (0-1)	
Rate ratio (95% CI)	NA	1.27 (0.64, 2.53)	0.78 (0.38, 1.62)	0.60 (0.33, 1.08)
P	NA	.49	.50	.09
Time from randomization to next platelet transfusion, median (IQR), d	3 (2-3)	3 (2-4)	3 (3-4)	
Hazard ratio (95% CI)	NA	0.85 (0.47, 1.55)	0.68 (0.36, 1.28)	0.81 (0.49, 1.34)
P	NA	.60	.23	.42

Differences in means are high response vs low response.

shown that differences between control and treated units are more pronounced with increasing number of platelet transfusions,[25] and we therefore cannot exclude that differences between groups in our study may have been observed if patients received multiple transfusions. We also cannot exclude the potential influence of previous nontrial transfusions on the outcomes measured.

An important limitation to the generalizability of our data is that we assessed stable nonbleeding patients requiring platelets for prophylaxis. We cannot extrapolate these data to patients actively bleeding at the time of transfusion, where the immediate hemostatic effectiveness of platelets might be more important than the ability to remain in the circulation. It is conceivable that platelets from high-responder donors could be the product of choice for bleeding patients, but this can only be elucidated by further research. The role of genetic factors in determining aspects of platelet function that may be important in disease states, as well as platelet storage and the outcome from transfusion, warrants further study.

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Authorship

Contribution: S.F.G., B.C.K., A.M.K., and W.H.O. designed the donor study and performed testing; A.M.K., R.A.C., B.C.K., T.R.G., N.H., S.F.G., A.D., L.B., C.L., T.F., L.M.W., and W.H.O. were responsible for PROmPT (Platelet Responsiveness and Outcome from Platelet Transfusion) study design and protocol; T.R.G., B.C.K., A.M.K., R.A.C., S.F.G., and A.D. performed statistical analysis and designed the statistical analysis plan; A.M.K. and N.H. were responsible for patient recruitment; L.B., C.L., A.D., and A.M.K. designed the database; and A.M.K., R.A.C., T.R.G., B.C.K., S.F.G., C.L., A.D., L.B., T.F., L.M.W., and W.H.O. wrote the manuscript.

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