Received: 24 February 2017 | Accepted: 11 April 2017

DOI: 10.1002/rth2.12004

ORIGINAL ARTICLE

WILEY rpth research and practice in thrombosis and haemostasis | ISTH

The association between platelet transfusions and bleeding in critically ill patients with thrombocytopenia

Donald M. Arnold MD[1,2] | Francois Lauzier MD[3] | Martin Albert MD[4] | David Williamson PhD[5] | Na Li PhD[6] | Ryan Zarychanski MD[7] | Chip Doig MD[8] | Lauralyn McIntyre MD[9] | Andreas Freitag MD[6] | Mark Crowther MD[1,10] | Lois Saunders [11] | France Clarke RRT[11] | Rinaldo Bellomo MD[12] | Ismael Qushmaq MD[13] | Renato D. Lopes MD[14] | Diane Heels-Ansdell MSc[11] | Kathryn Webert MD[2] | Deborah Cook MD[1] | For the PROTECT Investigators, the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group

[1]Department of Medicine and Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada

[2]Canadian Blood Services, Hamilton, Ontario, Canada

[3]Medicine, Centre hospitalier affilie universitaire de Quebec Hopital de l'Enfant-Jesus, Quebec City, Quebec, Canada

[4]Medicine, Hopital du Sacre-Coeur de Montreal, Montreal, Quebec, Canada

[5]Faculty of Pharmacy, Uiversite de Montreal, Montreal, Quebec, Canada

[6]Medicine, McMaster University, Hamilton, Ontario, Canada

[7]Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

[8]Departments of Critical Care Medicine and Internal Medicine, University of Calgary, Calgary, Alberta, Canada

[9]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[10]Department of Pathology and Molecular Medicine and Medicine, McMaster University, Hamilton, Ontario, Canada

[11]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada

[12]Austin Hills Hospital, Intensive Care, Melbourne, Australia

Abstract

Background: Platelet transfusions are commonly used to treat critically ill patients with thrombocytopenia. Whether platelet transfusions are associated with a reduction in the risk of major bleeding is unknown.

Patients/Methods: Observational cohort study nested in a previous multicenter, randomized thromboprophylaxis trial in the intensive care unit (ICU). The objective was to evaluate the association between platelet transfusions and adjudicated major bleeding events. Platelet transfusion episodes were reviewed for timing of administration, product type, and dose. Major bleeding with and without platelet transfusions was adjusted for severity of thrombocytopenia, use of anti-platelet agents, surgery and other covariates. Secondary outcomes were thrombosis, death in ICU and platelet count increment.

Results: Among 2,256 patients, 71 (3.1%) received 190 platelet transfusions. Of those, 121 (63.7%) were administered to 54 non-bleeding, thrombocytopenic patients. Adjusted rates of major bleeding were not statistically different with or without the administration of platelet transfusions (hazard ratio for transfused patients 0.85; 95% confidence interval, 0.42-1.72). We did not find a significant association between platelet transfusion use and thrombosis or death in ICU in adjusted analyses. Thrombocytopenia, anemia, major or minor bleeding and use of anticoagulants were associated with platelet transfusion administration. The median post-transfusion platelet count increment was 20×10^9/L at 3.5 hours post-transfusion.

[13]Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[14]Duke University Medical Center, Durham, North Carolina, USA

Correspondence
Donald M. Arnold, Medicine, McMaster University, Hamilton, ON, Canada.
Email: arnold@mcmaster.ca

Conclusions: Rates of major bleeding were not different for patients who did and did not receive platelet transfusions. Inferences were limited by the small number of transfused patients. Clinical trials are needed to better investigate the potential hemostatic benefit and potential harms of platelet transfusions for this high-risk population.

KEYWORDS
critical care, hemorrhage, mortality, platelets, thrombocytopenia, transfusion

Essentials

- Platelet transfusions are commonly used to treat critically ill patients with thrombocytopenia.
- Observational cohort study nested in a previous randomized trial in the intensive care unit.
- Major bleeding was not different in thrombocytopenic patients who did or did not get platelets.
- Thrombocytopenia, anemia, and anticoagulants were associated with platelet transfusion use.

1 | INTRODUCTION

Thrombocytopenia is common among critically ill patients[1–3] and platelet transfusions are often used to increase the platelet count in patients admitted to the intensive care unit (ICU). However, the effect of platelet transfusions on clinical outcomes, especially bleeding prevention, has not been well described in this population.[4] One reason is that bleeding occurrences in the ICU are dynamic and the measurement of major bleeding requires frequent, prospective assessments using population-specific measurement tools. In other patient groups such as hematology/oncology patients, the benefit of prophylactic platelet transfusions has been demonstrated in randomized trials.[5,6] No such data are available for critically ill patients, who often receive this treatment in the context of an increased bleeding risk due to surgery of frequent invasive procedures.[7] A recent systematic review highlighted the lack of ICU-specific data and identified the urgent need for platelet transfusion studies with clinical endpoints in this population.[8]

Platelet transfusions are also associated with harms, including well-accepted risks of transfusion-transmitted infection, allergic reactions, and inflammatory responses. In addition, they have been linked to the occurrence of venous thrombosis,[9] arterial thrombosis[10] and infection[11] in critically ill patients. Some studies have reported an association between platelet transfusions and mortality, but whether transfusion truly increases the risk of death or is a marker of the severity of the underlying illness is unclear.[10,12] A better understanding of the clinical benefits and potential harms of platelet transfusions is essential to justify whether and how this common treatment should be used.[13]

The primary objective of this study was to evaluate the association between platelet transfusions and major bleeding in critically ill patients. We used data from a large international thromboprophylaxis trial (PROTECT, clinicaltrials.gov NCT00182143) in which bleeding data were collected daily prospectively using an ICU-specific bleeding assessment tool. Patients were recruited from 2006 to 2010. Secondary objectives were to assess potential harms of transfusion, including thrombosis and death; factors associated with platelet transfusion administration; and platelet count increments following transfusion.

2 | METHODS

2.1 | Patients

We conducted an observational cohort study nested in a previous multinational, concealed, stratified, randomized, and blinded thromboprophylaxis trial called PROTECT, which enrolled 3,764 medical-surgical critically ill patients in 67 ICUs; results were published elsewhere.[14] For this sub-study, we included all PROTECT patients from Canadian centers only to ensure consistency of platelet transfusion products and to maximize feasibility. Patients enrolled in the main trial were ≥18 years old, weighed ≥45 kg, and had an expected ICU stay ≥72 hours. Reasons for exclusion were major hemorrhage in the previous week; admission following neurosurgery, trauma or orthopedic surgery; uncontrolled hypertension; ischemic stroke or intracranial hemorrhage in the last 3 months; pregnancy; history of heparin-induced thrombocytopenia; contraindications to blood products; and palliative care or limitation of life support. Patients who had platelet counts ≤50×10^9/L or severe coagulopathy (international normalized ratio [INR] or partial thromboplastin time [PTT] time ≥2 times the upper limit of normal) at the time of screening were also excluded.

We prospectively collected demographic and baseline clinical information including age, acute physiology and chronic health evaluation (APACHE) II score, admission diagnosis, and comorbid conditions. Daily data collected included complete blood cell counts, administration of blood products, life supports (eg, mechanical ventilation, inotropes or vasopressors, renal replacement therapy), surgical procedures (including any surgeries in the operating room and procedures occurring in the ICU [eg, tracheostomy], excluding central venous catheter or chest tube insertions); incident deep vein thrombosis and pulmonary embolism, anticoagulants and antiplatelet agents, and bleeding. Platelet transfusions were designated as prophylactic if they were given to prevent bleeding or therapeutic if they were given to

treat bleeding. Bleeding was assessed daily by a dedicated research coordinator using a validated bleeding assessment tool developed for the ICU.[15] Major bleeding was defined as hemorrhage at a critical site (eg, intracranial hemorrhage), that led to any of an invasive therapeutic intervention (eg, surgical intervention), hemodynamic compromise, transfusion of at least 2 units of red cells, or death. Minor bleeding was overt bleeding that did not meet criteria for major bleeding. Two independent, blinded investigators adjudicated all bleeding events with high reliability.[16]

A supplementary chart review of all patients who received one or more platelet transfusions was done by a transfusion medicine specialist (DMA). Blood bank records were verified and dose and type of platelet products (eg, apheresis, pooled whole blood platelets, or pooled buffy coat platelets) were adjudicated. A single platelet transfusion was defined as one adult dose of a platelet concentrate, which consisted of either 4-6 pooled random donor platelets or one unit of a single-donor platelet concentrate collected by apheresis. We recorded the available platelet count levels closest to and before the start of each transfusion, and closest to and after the end of each transfusion. The ABO blood group of the recipient and donor were also recorded. Participating centers submitted platelet transfusion records as source documents. This study was approved by the research ethics boards at each participating center.

2.2 | Statistical analysis

We compared demographic variables among patients who did and did not receive platelet transfusion(s) using the Mann-Whitney *U* test for continuous variables or Chi-square or Fisher's Exact test for categorical variables. We analyzed the association between prophylactic platelet transfusions and major bleeding using a multivariable Cox proportional hazards model for recurrent events, adjusted for age, treatment group in the main trial (unfractionated heparin [UFH] or dalteparin), use of antiplatelet agents, surgery, platelet count ($\geq 150\times10^9$/L; 100-149$\times10^9$/L; 50-99$\times10^9$/L; and $<50\times10^9$/L) and hemoglobin level. If the proportional hazards assumption did not hold for a discrete variable, it was used as a stratification variable. We assumed that the effect of a prophylactic transfusion lasted for 5 days based on the expected survival time of transfused platelets in circulation; thus, in the model, this time-varying variable would "switch on" immediately after the transfusion and "switch off" 5 days later. We used two models to investigate the association between prophylactic platelet transfusions and major bleeding events. In the first model, patients were considered at risk from the time of ICU admission until the time of discharge from ICU or death. In the second model, patients were considered at risk from the time of admission to the time of the first major bleed, discharge from ICU, or death.

We considered similar stratified multivariate Cox regression analyses to investigate the association between platelet transfusions and death in ICU, and platelet transfusions and thrombosis, adjusted for age, gender, APACHE II score, treatment assignment (UFH or dalteparin), mechanical ventilation, vasopressor or inotrope use, platelet count, hemoglobin level, and INR.

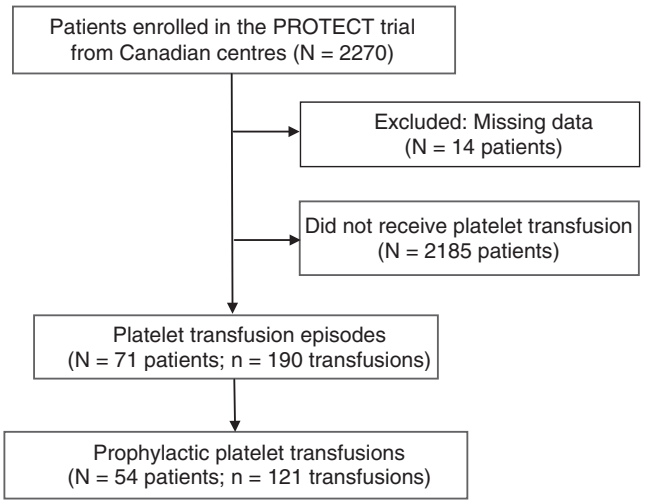

FIGURE 1 Patients from the PROTECT trial, a randomized thromboprophylaxis trial in critically ill patients, and platelet transfusions analyzed in this study

A separate regression analysis was done to evaluate factors associated with platelet transfusion administration adjusted for age, bleeding (major or minor), surgery, treatment assignment (UFH or dalteparin), use of antiplatelet or anticoagulant medications, platelet count, hemoglobin level. For each transfusion episode, we calculated the platelet count increment using the difference in platelet count levels before and after each transfusion. Using a multivariate generalized estimating equation model to account for multiple transfusions administered to the same patient, we determined patient and product-specific variables that influenced the platelet count increment.

3 | RESULTS

Among the 2,270 patients recruited from 35 Canadian centers in the PROTECT trial, 71 (3.1%) patients from 23 Canadian centers received 190 platelet transfusions (Figure 1). The median number of platelet transfusions per patient was 2 (Interquartile range [IQR] 1, 3). Most platelet transfusions (121/190; 63.7%) were administered prophylactically to prevent bleeding. In unadjusted analyses, patients who received platelet transfusions had a lower nadir platelet count (median 33×10^9/L vs 167×10^9/L) and a higher mean APACHE II score (25.6 ± 6.7 vs 21.8 ± 7.7), were more likely to have one or more major bleed at any time (47.9% and 5.3%) and were more likely to die in ICU (50.0% and 14.4%) compared with non-transfused patients (Table 1).

3.1 | Patient-level analyses

In our adjusted regression model which considered all prophylactic platelet transfusions, there was no statistically significant difference in the rate of major bleeding for patients who received prophylactic platelet transfusions (HR = 0.85, 95% CI 0.42-1.72; Table 2); but the effect was in the direction of bleeding avoidance. Similar results were

TABLE 1 Baseline and time-varying characteristics in critically ill patients from Canadian centers in the PROTECT trial who did receive platelet transfusion and other patients who did not

	Patients who received transfusion (n = 71)	Patients did not receive transfusion (n = 2185)	*P* value
Age (mean ± SD)	62.5 ± 15.4	60.9 ± 16.2	.406
Female, N (%)	25 (35.2)	928 (42.5)	.223
APACHE II score (mean ± SD)	25.6 ± 6.7	21.8 ± 7.7 (2184)	<.001
Laboratory results during hospitalization (mean±SD)			
INR (highest)	1.8 ± 0.8	1.5 ± 0.9	<.001
PTT (seconds) (highest)	82.7 ± 48.6	48.1 ± 30.3	<.001
Hemoglobin (g/L) (lowest)	65.8 ± 10.5	87.7±18.4	<.001
Creatinine (umol/L) (highest)	296.1 ± 185.1	169.4 ± 164.3	<.001
Platelets ($\times 10^9$/L) (lowest)	46.0 ± 47.0	182.6 ± 98.5	<.001
Lowest Platelet count ($\times 10^9$/L) during hospitalization, no. (%)			
<30	31 (43.7)	21 (1.0)	<.001
30-49	16 (22.5)	48 (2.2)	
50-99	19 (26.8)	286 (13.1)	
100-149	3 (4.2)	556 (25.4)	
≥150	2 (2.8)	1274 (58.3)	
ICU interventions during hospitalization, no. (%)			
Inotropes/vasopressors	66 (93.0)	1167 (53.4)	<.001
Invasive mechanical ventilation	70 (98.6)	2000 (91.5)	.033
Non-Invasive mechanical ventilation	10 (14.1)	326 (14.9)	.85
Surgical procedure	37 (52.1)	411 (18.8)	<.001
Hospital mortality (N, %)	40/70 (57.1)	499 (22.8)	<.001
ICU mortality (N, %)	35/70 (50.0)	314 (14.4)	<.001
Bleeding events, no. (%)	47 (66.2)	294 (13.5)	<.001
Major bleed	34 (47.9)	115 (5.3)	<.001
Minor bleed	13 (18.3)	179 (8.2)	.003
Duration of ICU stay (days, median)	22 (IQR 12-32)	9 (IQR 5-15)	<.001
Duration of hospital stay (days, median)	30 (IQR 15-53)	21 (IQR 11-43)	.027
Patients who received other transfusions (N, %)			
Red blood cell	69 (97.2)	745 (34.1)	<.001
Frozen plasma	48 (67.6)	178 (8.2)	<.001
DVT or PE, no. (%)	25 (35.2)	338 (15.5)	<.001
In ICU	25 (35.2)	298 (13.6)	<.001
Post-ICU	0	55 (2.5)	–

ICU, intensive care unit; IQR, interquartile range; DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; PTT, partial thromboplastin time.

obtained when patients were censored after the first major bleed (HR = 0.90, 95% CI 0.30-2.70). These analyses were underpowered (power = 21%)[17,18] as the number of patients who received platelet transfusions was relatively small. When we restricted the analysis to patients with a nadir platelet count less than 50×10^9/L, we identified 33 patients who did and 69 patients who did not receive platelet transfusions (median nadir platelet counts were 31×10^9/L [IQR 20-39$\times10^9$/L] and 38×10^9/L [IQR 26-45$\times10^9$/L], respectively). Three (9.1%) transfused patients developed major bleeding within 5 days compared with 14 (20.3%) non-transfused patients (OR = 0.39, 95% CI 0.10-1.48).

In our analysis of the association between platelet transfusions and venous thrombosis, there was a trend towards harm but no significant association (HR = 1.23, 95% CI 0.76-1.99). Similarly, there was no significant association between platelet transfusions and death in ICU in our adjusted analysis (HR = 0.93, 95% CI 0.54-1.60) (Table 3); however, the effect was in the direction of a survival advantage.

TABLE 2 Predictors of major bleeding events, including prophylactic platelet transfusions (Cox regression, recurrent event analysis[a])

Risk factor	Hazard ratio (95% CI)
Prophylactic platelet transfusion	0.85 (0.42, 1.72)
Treatment group (UFH vs dalteparin)	1.11 (0.73, 1.68)
Anti-platelet medications	1.10 (0.67, 1.82)
Platelet count	
50-99 vs <50×10^9/L	1.75 (0.96, 3.20)
100-149 vs <50×10^9/L	1.19 (0.62, 2.31)
≥150 vs <50×10^9/L	0.32 (0.17, 0.60)

CI, confidence interval; UFH, unfractionated heparin.
[a]Adjusted for age, treatment group in the main trial (unfractionated heparin or dalteparin), use of antiplatelet agents, surgery, platelet count and hemoglobin level.

TABLE 3 Predictors of mortality (multivariate Cox regression analysis[a])

Risk factor	Hazard ratio (95% CI)
Platelet transfusion	0.93 (0.54, 1.60)
UFH vs dalteparin	0.90 (0.70, 1.14)
APACHE II	1.03 (1.01, 1.05)
Platelet count	
50-99 vs <50×10^9/L	0.74 (0.41, 1.35)
100-149 vs <50×10^9/L	0.57 (0.31, 1.04)
≥150 vs <50×10^9/L	0.40 (0.23, 0.72)
Hemoglobin	
83-100 vs >100 g/L	0.80 (0.59, 1.09)
≤82 vs >100 g/L	0.65 (0.45, 0.93)

CI, confidence interval; UFH, unfractionated heparin.
[a]Adjusted for age, gender, APACHE II score, treatment assignment (UFH or dalteparin), mechanical ventilation, vasopressor or inotrope use, platelet count, hemoglobin level and INR.

3.2 | Transfusion-level analyses

For all platelet transfusions, pre-transfusion platelet counts were <30×10^9/L (n = 43, 22.6%); 30-50×10^9/L (n = 48, 25.3%); 50-100×10^9/L (n = 78, 41.1%); 100-150×10^9/L (n = 9. 4.7%) and >150×10^9/L (n = 12, 6.2%). Platelet transfusion products were apheresis (59/186; 31.7%), buffy coat (n = 58/186; 31.2%), or whole blood-derived pooled platelet concentrates (69/186; 37.1%; Table S1). Platelet product information was missing for 4 transfusions. Platelet transfusions were incompatible with the ABO blood group of the recipient for 30 patients (15.9%).

Factors associated with platelet transfusion administration were thrombocytopenia, especially platelet counts <50×10^9/L (HR = 38.15, 95% CI 18.48-78.78); anemia (HR = 1.38, 95% CI 1.19-1.61); major or minor bleeding (HR = 2.79, 95% CI 1.62-4.82); and the use of anticoagulants (HR = 2.19, 95% CI 1.16-4.13) (Table 4).

TABLE 4 Determinants of platelet transfusion administration (multivariate Cox regression analysis[a])

Risk factor	Hazard ratio (95% CI)
Therapeutic anticoagulation	2.19 (1.16, 4.13)
Anti-platelet medications	0.68 (0.41, 1.13)
Hemoglobin (per 10g/L drop)	1.38 (1.19, 1.61)
Platelet count	
<50 vs ≥100×10^9/L	38.15 (18.48, 78.78)
50- 99 vs ≥100×10^9/L	170.22 (78.73, 368.00)
Bleeding (minor or major)	2.79 (1.62, 4.82)

CI, confidence interval.
[a]Adjusted for age, bleeding (major or minor), surgery, treatment assignment (unfractionated heparin or dalteparin), use of antiplatelet or anticoagulant medications, platelet count and hemoglobin level.

Of the 33 non-bleeding patients with a platelet count less than 50×10^9/L, 32 patients received 54 individual prophylactic platelet transfusions with pre- and post-transfusion platelet counts available. The median platelet count increment was 21.5×10^9/L (IQR 13-34) as measured 4.9 hours (IQR 2.7-9.5) after the transfusion. Similar results were obtained when all platelet transfusions were analyzed (n=156 individual transfusions for 65 bleeding and non-bleeding patients): Median platelet count increment was 20×10^9/L (IQR 8.5-33) measured 3.5 hours (IQR 1.9-6.8) after the transfusion. Platelet count increments were generally short-lived, lasting less than 12 hours (Figure 2). Receipt of a second platelet transfusion on the same day (P<.001) and a pre-transfusion platelet count ≥100 ×10^9/L (P=0.015) were associated with smaller platelet count increments.

4 | DISCUSSION

In this sub-study of a large randomized trial, we found that prophylactic platelet transfusions administered to critically ill patients with thrombocytopenia were not associated with a reduction in the risk of major bleeding compared to non-transfused thrombocytopenic patients. The number of transfused patients was small which limits the inferences one can make based on these data, and raises the possibility of spurious results including a type II error concluding that platelets do not prevent bleeding when they actually do. Indeed, the direction of the effect favored bleeding prevention, however the effect size was small, and perhaps substantially smaller than intensivists may anticipate when transfusing platelets in the ICU. This study, despite its modest sample size, is unique in that we examined bleeding outcomes after platelet transfusions in ICU patients using validated bleeding data that were collected prospectively on a daily basis. Assuming that the risk of major bleeding in non-transfused ICU patients with severe thrombocytopenia (platelets <50×10^9/L) is ~20%[15,19], and the risk of major bleeding in transfused patients is ~10%, we estimated that a randomized trial of prophylactic platelet transfusions in this setting

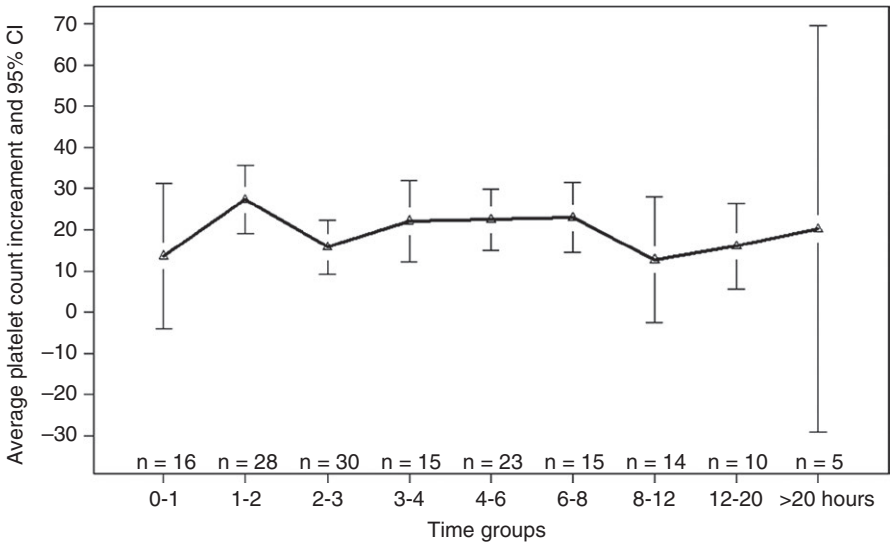

FIGURE 2 Average platelet count increment and 95% confidence interval at specified times after the transfusion

would require several thousand patients, depending on the ICU type and adjustment for covariates.

Thrombocytopenia is a common complication of critical illness with a prevalence on ICU admission of up to 64% and an incidence over the ICU stay of up to 34%.[3] The cause of thrombocytopenia in this setting is multifactorial[4] often related to bone marrow suppression from acute illness or infection, platelet consumption associated with disseminated intravascular coagulation or circulatory bypass or dilution from major fluid shifts. Rarely is a drug reaction or a primary hematological disorder the cause. ICU-acquired thrombocytopenia has been associated with clinical outcomes including major bleeding, blood transfusions, and death[1]; however, whether platelet transfusions can mitigate the risk of these events is unclear.

In 2015, the National Heart, Lung, and Blood Institute identified several key priority research questions in the clinical practice of transfusion medicine. Among them were the safety and efficacy of prophylactic platelet transfusions before common invasive procedures and the clinical consequences of ABO matching in diverse patient groups including critical care.[13] Our study begins to address some of these issues. We found no significant difference in the risk of major bleeding among thrombocytopenic patients who did and did not receive a platelet transfusion; however, further prospective controlled trials are needed.

We did not identify a significant association between platelet transfusions and thrombosis, although there was a trend towards harm. This finding is consistent with a previous study conducted in a similar medical-surgical ICU population, which showed that platelet transfusion increased the risk of venous thrombosis.[9] In a recent study using data from a national hospital discharge database in the United States, investigators reported that platelet transfusions were associated with an increased risk of in-hospital death in patients with thrombocytopenia due to heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura.[10] Those conditions are inherently pro-thrombotic and the study did not adjust for platelet count levels; thus, the results are not readily generalizable to a broader ICU population. In other studies, platelet transfusions were associated with an increased risk of death among patients undergoing liver transplantation[12] and cardiac surgery[20]; however, these results derive from non-randomized data confounded by illness severity. Our results do not clearly show a survival benefit, but the confidence intervals were wide and underscore how larger studies are needed to confirm or refute any such association.

Additional findings in this study were that a single platelet transfusion episode would be expected to raise the platelet count by approximately 20×10^9/L, which is consistent with other ICU studies.[7,21] The platelet count increment was most pronounced within a few hours and the effect was generally short lived. The need for multiple transfusions and a high pre-transfusion platelet count ($\geq100\times10^9$/L) were associated with a smaller platelet count increment post transfusion. In this study, an ABO blood group incompatibility between donor and recipient was not associated with a smaller platelet count increment; however, this analysis was underpowered. In a previous ICU study which included predominantly cardiac surgery patients, ABO incompatibility was a significant predictor of poor platelet count increment.[7] It is evident that the anticipated platelet count increment after a platelet transfusion depends on the population and the underlying cause of the thrombocytopenia.

A key strength of this study was the rigorous assessments of bleeding–the most critical outcome in platelet transfusion studies. Unlike many other studies in this field, bleeding data were collected prospectively, on a daily basis, using a clinically useful, ICU-specific, validated bleeding tool with high inter-rater reliability.[15] We used a blinded adjudication process for all major bleeds, which demonstrated high agreement.[16] Other strengths were our analysis of the association between prophylactic platelet transfusions and major bleeding, which was adjusted for variables known to be related to this outcome.[19] Enrolment of a heterogeneous group of medical-surgical patients from 23 Canadian centers enhances the generalizability of our findings to hospitals with similar methods of blood collection and transfusion.

Limitations were the small number of patients with incident severe thrombocytopenia (platelet count $<30\times10^9$/L) who would be expected to benefit most from platelet transfusions. Patients with baseline platelet counts $<50\times10^9$/L and who were bleeding at the time

of screening for the main trial were excluded, which may have underestimated the effect of platelet transfusions on bleeding outcomes. The protective effect of platelets in frail ICU patients with pre-existing hemostatic impairments may be more pronounced. Although we adjusted for factors that we believe may influence bleeding risk, our analysis cannot replace direct, real-time, daily clinical risk assessments in a dynamic ICU environment. Patients in this cohort were mostly medical; however, platelet transfusions were more commonly administered to surgical patients. Thus, our results may not apply to a predominantly surgical or trauma population who may have different platelet requirements. For example, for patients undergoing cardiac surgery, platelet dysfunction due to anti-platelet medications or bypass circuits is common. A platelet transfusion study in that population would need to consider these other bleeding risks in addition to absolute platelet count levels for study entry.

These results contribute to the modest information base in transfusion medicine relevant to the care of critically ill patients. In this setting, most platelet transfusions were administered to prevent rather than to treat bleeding; however, the effect of this intervention on bleeding avoidance and other clinical endpoints remains uncertain. Our data emphasizes the need for randomized trials of platelet transfusions in the ICU.

ACKNOWLEDGMENTS

Author Contributions: D. Arnold conceived the research, collected the data, analyzed the data, interpreted the results and wrote the manuscript; F. Lauzier conceived the research, interpreted the results and wrote the manuscript; M. Albert conceived the research, interpreted the results and wrote the manuscript; D. Williamson conceived the research, interpreted the results and wrote the manuscript; N. Li analyzed the data, interpreted the results and edited the final version of the manuscript; R. Zarychanski interpreted the results and edited the final version of the manuscript; C. Doig interpreted the results and edited the final version of the manuscript; L. McIntyre interpreted the results and edited the final version of the manuscript; A. Freitag interpreted the results and edited the final version of the manuscript; M. Crowther conceived the research, interpreted the results and edited the final version of the manuscript; L. Saunders collected the data, analyzed the data and edited the final version of the manuscript; F. Clarke collected the data and approved the final version of the manuscript; R. Bellomo interpreted the results and edited the final version of the manuscript; I. Qushmaq collected the data and approved the final version of the manuscript; R. Lopes interpreted the results and edited the final version of the manuscript; D. Heels-Ansdell analyzed the data, interpreted the results and wrote the manuscript; K. Webert conceived the research, interpreted the results and edited the manuscript; and D. Cook conceived the research, collected the data, analyzed the data, interpreted the results and wrote the manuscript.

We are grateful to Rob Fowler and Claudio Martin for constructive feedback on earlier drafts of this manuscript. We thank Genie LeBlanc and Nicole Zytaruk for their assistance coordinating the study; Yang Liu for statistical oversight; and Shannon Lane for help with formatting the paper.

The authors wish to thank the Canadian Investigators and Research Coordinators for their help with this study: Rick Hall, Graeme Rocker, Lisa Julien, Debbie Wright, Caroline Roy, Judy Theriault, Susan Pleasance (QE II Health Science Centre); Maureen Meade, Lois Saunders, Lori Hand (Hamilton HSC, General Site); Andreas Freitag, Lois Saunders, Christine Wynne, Mark Duffett, Michelle Kho, Nicole Zytaruk (Hamilton HSC, McMaster Site); John Granton, Andrea Matte, Paulina Farias, Leslie Chu, Nancy Brockest, Stephanie Go, Margaret McGrath-Chong, Madison Dennis, Marc Lipkus, Emily Stern, Ryan Albert (University Health Network, General Site); Francois Lauzier, Stephan Langevin, Alexis F Turgeon, Marie-Claude Tremblay, Martine Blais, Maxime Beauparlant, Julie Asselin, Caroline Roy, Chantal Gagne, Marie Thibodeau (Centre Hospitalier Affilie-Enfant Jesus); Germain Poirier, Sandrine Spearson, Isabelle Neas (Hopital Charles LeMoyne); Joe Pagliarello, Lauralyn McIntyre, Paul Hébert, Irene Watpool, Tracy McArdle, Claude Gaudert, Paule Marchand, Carson Davidson, Mary-Jo Lewis, Erin Murphy, Julia Foxall (Ottawa Hospital, Civic Site and General Site); Yoanna Skrobik, Johanne Harvey, Stefania Chitu (Hopital Maisonneuve, Rosemont); Martin Albert, David Williamson, Virginie Williams, Carole Sirois, Carole Nadon, Stephanie Dolle, Audrey-Anne Gosselin, Patrice Deroy (Hopital Sacre Coeur); Geeta Mehta, Sumesh Shah, Cheryl Ethier, Sam Tirgari, Lindsay Steinberg, Rod McDonald, Vidhya Sivanantham, Kristofer Bandayrel, Friederike Quittnat Pelletier, Marnie Kramer-Kile, Maedean Brown, Scott Kim (Mount Sinai Hospital); Rob Fowler, Nicole Marinoff, Karen Code, Boris Bojilov, Derek Parsotam (Sunnybrook Hospital); John Marshall, Orla Smith, Beth Fry, Kerri Porretta, Yoon Lee, Jeanna Morrissey, Victoria Wen (St. Michael's Hospital); John Muscedere, Miranda Hunt, Susan Fleury, Nicole Godfrey, Sharlene Hammond, Elizabeth Mann, Monica Myers, Amber Robinson (Kingston General Hospital); Donald Griesdale, Dean Chittock, Vinay Dhingra, Denise Foster, Maureen Gardner, Susan Logie, Roger Autio, Dara Davies, Pia Ganz, Laurie Smith (Vancouver General Hospital); Peter Dodek, Victoria Alcuaz, Betty Jean Ashley, Sheilagh Mans (St. Paul's Hospital); John Granton, Niall Ferguson, Andrea Matte, James Stevenson, Joel Elman, Madison Dennis (University Health Network, Western Site); Timothy Karachi, Tina Millen, Andrea Tkaczyk (Hamilton HSC, Juravinski Site); Mike Jacka, Marleen Irwin, Carmen Chan, Leeca Sonnema, Kelly Marsh, Jennifer Maurer, Tamara Kreidl, Candice Varden, Carey Kinjerski (University of Alberta Hospital, General); Christopher Doig, Stacy Ruddell, Linda Knox, Crystal Wilson, Kevin Champagne (The Peter Lougheed Hospital); Gordon Wood, Fiona Auld, Leslie Atkins (Vancouver Island Health Authority); Ryan Zarychanski, Bojan Paunovic, Nicole Marten, Kym Wiebe (St. Bonafice Hospital); Deborah Cook, France Clarke, Nicole Zytaruk, Ellen McDonald, Andrea Tkaczyk (St. Joseph's Healthcare).

We also appreciate the help of other international PROTECT Trial Investigators and Research Coordinators:

Canadian Investigators

Drs. Sean Keenan & Steven Reynolds, Miroslav Svetik, Mary Van Osch (Royal Columbian Hospital, Westminster); Dr. Chip Doig, Linda Knox, Crystal Wilson, Kevin Champagne (Calgary University Foothills Hospital, Calgary); Dr. Jim Kutsogiannis, Patrica Thompson, Norine Whalen (Royal Alexandra Hospital, Edmonton); Dr. Francois Lellouche,

Marie-Claude Ferland, Patrick Dussault, Caroline Jacob, Marie-Eve Morneau, Nancy Laberge (Laval Hospital, Quebec City); Dr. Kosar Khwaja, Laura Banici, Carole Sirois, Lena Havell (Montreal General Hospital, Montreal); Drs. Olivier Lesur & Francois Lamontagne, Sandra Proulx (Sherbrooke University Hospital and Centre de Recherche Clinique Étienne-Le Bel, Sherbrooke); Dr. Kosar Khwaja, Laura Banici, Carole Sirois, Lena Havell (Royal Victoria Hospital, Montreal); Drs. Gerald Hollinger & Vasanti Shende, Vanessa Belcastro (Guelph General Hospital, Guelph); Dr. Bill Plaxton, Anders Foss (Grand River Hospital, Kitchener); Dr. Jonathan Eisenstat, Tammy Doerle (Lakeridge Health, Oshawa); Drs. Steven Reynolds & Sean Keenan, Sheilagh Mans (Surrey Memorial Hospital, Surrey); Dr. Michael Sharpe, Mona Madady (London Health Sciences Center, London).

Australian Investigators

Drs. Jamie Cooper (Lead) & Andrew Davies, Shirley Vallance, Cindy Weatherburn, Jasmin Board, Victoria Bennett (Alfred Hospital, Melbourne); Drs. Simon Finfer & Naresh Ramakrishnan (deceased), Simon Bird, Julie Potter, Anne O'Connor, Susan Ankers (Royal North Shore Hospital, Sydney); Dr. Jack Cade, Deborah Barge, Tania Caf, Belinda Howe (Royal Melbourne Hospital, Melbourne); Dr. Rinaldo Bellomo, Glenn Eastwood, Leah Peck, Donna Goldsmith, Kim O'Sullivan (Austin Hospital, Melbourne); Drs. David Ernest, Sam Radford, Ann Whitfield & Anthony Cross, Suzanne Eliott, Jaspreet Sidhu, Belinda Howe, Inga Mercer, Angela Hamilton (deceased) (Box Hill Hospital, Melbourne); Dr. John Botha, Jodi Vuat, Sharon Allsop, Nina Fowler (Frankston Hospital, Frankston); Drs. Tim Crozier, Jonathan Barrett & Chris Wright, Pauline Galt, Carly Culhane, Rebecca Ioannidis, Sue Burton, Marnie Reily, Cyveen Weeraratna (Monash Medical Centre, Melbourne); Dr. Ian Seppelt, Leonie Weisbrodt, Robyn Bond; Nepean Hospital, Sydney.

Dr. David Evans, Justine Rivett, Stephanie O'Connor, Alex Poole (Royal Adelaide Hospital, Adelaide); Dr. Clive Woolfe, Dorrilyn Rajbhandari, Caitlin Rees (Royal Prince Alfred Hospital, Camperdown); Drs. John Edington & Jason Fletcher, Julie Smith, Catherine Boschert (Bendigo Health Care, Bendigo); Dr. Graham Reece, Treena Sara, Kiran Nand (Blacktown Hospital, Blacktown); Drs. Andrew Bersten & Alex Gallus, Elisha Matheson, Margie O'Callaghan (Flinders Medical Center, Adelaide); Dr. Neil Orford, Tania Elderkin, Melissa Fraser, Allison Bone, Tania Salerno, Anne Kinmonth (Geelong Hospital, Geelong); Dr. Subhash Arora, Bridget O'Bree, Katherine Shepherd (Dandenong Hospital, Dandenong); Drs. Alan Davey–Quinn & Martin Sterba, Bronwyn Ruth Johnson, Renee Xu, Francisco Hill (Wollongong Hospital, Wollongong); Dr. Rajaram Ramadoss, Josette Wood (Lyell McEwin Hospital, Adelaide)

Brazilian Investigators

Dr. Marcelo Garcia da Rocha (Co-Lead), Andréa Kramer, Martha Hädrich (Santa Casa Hospital, Porto Allegre); Drs. Nilton Brandao, Cassiano Teixeira & Cíntia Roehrig, Juliana Zeni (Moinhos de Vento Hospital, Porto Alegre); Drs. Suzana Alves da Silva & Rubens Costa Filho, Renato Correa, Alves Moreira and Plínio N. Gomes & Rodrigo Biondi (Pró Cardíaco Hospital, PROCEP, Rio de Janeiro); Drs. Otavio Berwanger (Co-Lead) & Edson Romano, Anna Maria Buehler (Hospital Coracao Research Institute HCor, São Paulo); Drs. Helio Penna Guimarães & Renato D Lopes, Adriano Truffa, Rosana Nakamura, Lillian Mazza Barbosa (Hospital São Paulo, São Paulo)

Saudi Arabian Investigators

Dr. Ismael Qushmaq (Lead), Jean Brennick, Sawsan Bassi (King Faisal Specialist Hospital and Research Center, Jeddah); Dr. Mohammed Alsultan & Yaseen Arabi, Riette Brits (King Saud Bin Abdulaziz University for Health Sciences, Riyadh); Dr. Jamal Alhashemi, Sanaa Shalabi (King Abdulaziz University Hospital, Jeddah); Drs. Yasser Mandourah & Nadeem Shaikh (Riyadh Military Hospital, Riyadh); Drs. Manal Al-Hazmi & M. Ali Al-Azem, Trevor Wyngaard (King Fahad Medical City Hospital, Riyadh)

United States Investigators

Dr. James Klinger, Barbara Smithson (Rhode Island Hospital, Providence); Dr. Nicholas E Vlahakis (Lead), Laurie Meade (Mayo Clinic, Rochester); Dr. Michael Cox, Jackie O'Brien, Catherine Krause (St John's Mercy Medical Center, St Louis); Drs. Joseph Nates & Sajid Haque, Deidre Mooring, Rose Erfe, Paula Nickerson (University of Texas MD Anderson Cancer Center, Houston)

United Kingdom Investigators

Drs. Marlies Ostermann (Lead) & David Treacher, Tony Sherry, John Smith, Barnaby Sanderson, Josephine Ng, John Brooks, Ling Lim, Katie Lei (King's College London, Guy's & St Thomas' Hospital, London)

Financial support for this study was provided by Canadian Blood Services, the federal government of Canada (Health Canada) and provincial and territorial ministries of health. The views herein do not reflect the views of Canadian Blood Services or the federal, provincial, or territorial governments of Canada.

The original trial was funded by the Canadian Institutes of Health Research and the Australian and New Zealand College of Anesthetists Research Foundation. Prophylactic dalteparin drug was provided by Pfizer, Inc and Esai, Inc. None of these agencies played a role in the design, conduct, analysis, interpretation or write-up of the original trial or this study.

D Arnold holds the JG Kelton Chair in Translational Research from McMaster University. F Lauzier is a recipient of a research career award from the Fonds de la recherche du Québec-Santé. R. Zarychanski receives salary support from CIHR as a New Investigator. L McIntyre holds a New Investigator Award from the Canadian Institute of Health Research/Canadian Blood Services. M Crowther holds the Leo Pharma Chair in Thromboembolism Research at McMaster University and St Joseph's Healthcare, Hamilton. D Cook is a Research Chair of the Canadian Institutes of Health Research.

RELATIONSHIP DISCLOSURES

None of the authors have any disclosures relevant to this paper.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Arnold DM, Lauzier F, Albert M, et al. The association between platelet transfusions and bleeding in critically ill patients with thrombocytopenia. *Res Pract Thromb Haemost*. 2017;1:103–111. https://doi.org/10.1002/rth2.12004