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

Donald M. Arnold MD1,2 | Francois Lauzier MD3 | Martin Albert MD4 |
David Williamson PhD5 | Na Li PhD6 | Ryan Zarychanski MD7 | Chip Doig MD8 |
Lauralyn McIntyre MD9 | Andreas Freitag MD6 | Mark Crowther MD1,10 |
Lois Saunders11 | France Clarke RRT11 | Rinaldo Bellomo MD12 |
Ismael Qushmaq MD13 | Renato D. Lopes MD14 | Diane Heels-Ansdell MSc11 |
Kathryn Webert MD2 | Deborah Cook MD1 | For the PROTECT Investigators, the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group

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.
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INTRODUCTION

Thrombocytopenia is common among critically ill patients1–3 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 thrombosis10 and infection11 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.

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 ≤50×109/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 comorbidity 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, antiocoagulants 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.\textsuperscript{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.\textsuperscript{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 \textit{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 (\(\geq 150\times 10^9/L\); 100-149\(\times 10^9/L\); 50-99\(\times 10^9/L\); and <50\(\times 10^9/L\)) 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.

### 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\(\times 10^9/L\) vs 167\(\times 10^9/L\)) and a higher mean APACHE II score (25.6 \pm 6.7 vs 21.8 \pm 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
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%)\textsuperscript{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 20-39×10^9/L] and 38×10^9/L [IQR 26-45×10^9/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 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 (>10^9/L) (lowest) | 46.0 ± 47.0 | 182.6 ± 98.5 | <.001 |
| Lowest Platelet count (>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.
TABLE 2  Predictors of major bleeding events, including prophylactic platelet transfusions (Cox regression, recurrent event analysis)

| 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.

*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)

| 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.

*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).

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%15,17, and the risk of major bleeding in transfused patients is ~10%, we estimated that a randomized trial of prophylactic platelet transfusions in this setting...
with clinical outcomes including major bleeding, blood transfusions, and death among patients undergoing liver transplantation and cardiac surgery; 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 $20 \times 10^9/L$, which is consistent with other ICU studies. 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 ($\geq 100 \times 10^9/L$) 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. 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. We used a blinded adjudication process for all major bleeds, which demonstrated high agreement. 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. 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 $<30 \times 10^9/L$) who would be expected to benefit most from platelet transfusions. Patients with baseline platelet counts $<50 \times 10^9/L$ 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.

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Australian Investigators

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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. Jalal Alhashemi, Sanaa Shalabi (King Abdulaziz University Hospital, Jeddah); Drs. Yasser Mandoraur & Nadeem Shaiikh (Riyadh Military Hospital, Riyadh); Drs. Manal Al-Hazmi & M. Ali Al-Azem, Trevor Wyngaard (King Fahad Medical City Hospital, Riyadh)

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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)

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RELATIONSHIP DISCLOSURES

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

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SUPPORTING INFORMATION
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Author/s:
Arnold, DM; Lauzier, F; Albert, M; Williamson, D; Li, N; Zarychanski, R; Doig, C; McIntyre, L; Freitag, A; Crowther, M; Saunders, L; Clarke, F; Bellomo, R; Qushmaq, I; Lopes, RD; Heels-Ansdell, D; Webert, K; Cook, D

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