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Platelet transfusions in adult thrombocytopenic ICU patients: protocol for a sub-study of the PLOT-ICU cohort

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Conflict of interest

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Abstract

(245/250 words recommended, 350 max)

Introduction

Platelet transfusions are frequently used in ICU patients, but contemporary epidemiological data are sparse. We aim to present contemporary international data on the use of platelet transfusions in adult ICU patients with thrombocytopenia.

Methods

This is a protocol and statistical analysis plan for a *post hoc* sub-study of 504 thrombocytopenic patients from the "Thrombocytopenia and platelet transfusions in ICU patients: an international inception cohort study (PLOT-ICU)". The primary outcome will be the number of patients receiving platelet transfusion in the ICU reported according to the type of product received (apheresis-derived vs. pooled whole-blood-derived transfusions). Secondary platelet transfusion outcomes will include platelet transfusion volumes; timing of platelet transfusion; approach to platelet transfusion dosing (fixed dosing vs. weight-based dosing) and platelet count increments for prophylactic transfusions. Secondary clinical outcomes will include the number of patients receiving red blood cell- and plasma transfusions during ICU stay; the number of patients who bled in the ICU, the number of patients who had a new thrombosis in the ICU, and the number of patients who died. The duration of follow-up was 90 days. Baseline characteristics and secondary clinical outcomes will be stratified according to platelet transfusion status in the ICU and severity of thrombocytopenia. Data will be presented descriptively.

Conclusions

The outlined study will provide detailed epidemiological data on the use of platelet transfusions in adult ICU patients with thrombocytopenia using data from the large international PLOT-ICU cohort study. The findings will inform the design of future randomised trials evaluating platelet transfusions in ICU patients.

Background

Thrombocytopenia (defined as platelet count <150x10^9 per L) frequently accompanies critical illness. Approximately 40% of adult intensive care unit (ICU) patients have thrombocytopenia upon arrival to the ICU or will develop it at some point during their ICU stay [1–4]. Thrombocytopenia has been associated with an increased risk of major bleeding in adult ICU patients [5–7] and platelet transfusions are often used in these patients to treat or prevent bleeding [3, 4, 8]. This makes ICUs major consumers of platelet transfusions, with reports indicating that 5-24% of all platelet transfusions are used in ICUs [9–11].

Previous studies reporting data on the use of platelet transfusions in adult ICU patients have primarily focused on indications for platelet transfusions, pre-transfusion platelet counts and post-transfusion platelet count increments [3, 8, 12–18]. Some studies have reported data from general ICU patients [8, 12–14, 17], but few have been international [13]. Data describing other important aspects of the epidemiology of platelet transfusions, such as the type of platelet product used (apheresis- vs. pooled whole-blood-derived), platelet transfusion volumes, method of dosing, and the timing of transfusion during ICU stay are scarce.

Platelet transfusions produced by apheresis are more costly than those produced from whole-blood donations [19] but reduce donor exposure, which, in theory, could lower alloimmunisation rates [20]. Although post-transfusion platelet counts may be higher with apheresis-derived products than with whole-blood-derived products, clinical benefits are uncertain [21, 22]. In the absence of evidence regarding the efficiency of different platelet products, the type of product used may often be at the discretion of the local blood banks and available stock [22]. Considerable variation in the use of apheresis- and whole-blood-derived platelet products in ICUs across different countries is therefore likely but remains to be elucidated.

Platelet transfusions constitute a limited resource; the short shelf time of platelets makes it challenging to maintain adequate stock, and demands have been projected to increase due to the ageing of the population [23, 24]. Further, the evidence from randomised clinical trials (RCTs) assessing the safety and efficacy of platelet transfusions in the ICU setting is limited to a recent non-inferiority trial assessing prophylactic platelet transfusions before central venous catheter (CVC) placement [25–27]. Additional trials evaluating the use of platelet transfusions in the ICU setting are highly warranted to ensure optimal use of platelet transfusions. The planning of RCTs requires a scientific workup, including data on current practice and characteristics and outcomes of the population that receives the intervention [28]. We recently conducted an international cohort study examining the frequencies of thrombocytopenia, use of platelet transfusions and outcomes in a broad adult ICU population [4, 29]. With this sub-study, our primary aim is to provide additional contemporary epidemiological data on the use of platelet transfusions in adult ICU patients with thrombocytopenia, including the type of product used, platelet transfusion volumes, method of dosing, timing of transfusion and post-transfusion platelet count increments. Second, we aim to describe characteristics and clinical outcomes in ICU patients with thrombocytopenia who received platelet transfusions in the ICU and in those who did not.

Research questions

In the PLOT-ICU study:

- How many adult patients with thrombocytopenia received apheresis- vs. pooled whole-blood-derived platelet transfusions in the ICU, and did it vary across countries?
- What was the average volume contained in a platelet transfusion, and did it vary across countries?
- What were the post-transfusion platelet count increments for prophylactic platelet transfusions used in the ICU?
- During which ICU days were platelet transfusions used, and how many platelet transfusions were used on these days?
- How many ICUs used a fixed dosing vs. weight-based dosing approach to platelet transfusions?
- Were patient characteristics similar between patients with thrombocytopenia receiving platelet transfusions in the ICU vs. those not receiving platelet transfusions?
- How many patients with thrombocytopenia received red blood cell transfusions, how many received plasma transfusions, how many bled in the ICU, how many had a new thrombosis in the ICU, and how many died? Were these numbers comparable between patients receiving platelet transfusions in the ICU vs. those not receiving platelet transfusions?

Methods

Design and setting

This is a protocol for a *post hoc* analysis of the PLOT-ICU study database. The PLOT-ICU study was an international prospective inception cohort study of 1166 ICU patients from 52 ICUs in 10 countries in Europe and the United States of America. Consecutive patients were enrolled at ICU admission during 14-day inception periods conveniently chosen by participating sites between May 2021 and July 2022 and were followed during their stay(s) in participating ICUs for a maximum of 90 days [4, 29].

Ethics and approvals

The PLOT-ICU study was approved by the Danish Centre for Regional Development (R-21012287) and registered at the Danish Capital Region's Legal Department for Research (P-2021-262). All necessary national/regional/local approvals were obtained as appropriate, and informed consent was sought from patients and/or relatives if required by applicable regulations [4, 29].

Population

All patients with thrombocytopenia (defined as platelet count $<150x10^9$/L at ICU admission and/or during ICU stay) enrolled in the PLOT-ICU study will be eligible for this sub-study [4]. The PLOT-ICU study enrolled adult (≥18 years of age) acutely admitted (i.e., a non-planned admission) patients regardless of diagnosis and expected length of ICU stay and excluded patients who denied informed consent, had previously been enrolled or underwent elective open-heart surgery during the hospitalisation leading to the ICU admission [4, 29].

Definitions and assumptions

We will use the same definitions and assumptions as done in the PLOT-ICU study [4, 29]. Below is a short description of concepts important to the current study.

Platelet transfusions

Apheresis-derived and pooled whole-blood-derived platelet transfusions were defined as platelet transfusions produced from a single donor by plateletpheresis and from platelet concentrates from multiple donors (by the buffy-coat method or platelet-rich-plasma method), respectively [20, 30]. Indications for platelet transfusions were defined as pre-procedural: covering invasive procedures or surgery; prophylactic: reducing bleeding risk; and therapeutic: treating bleeding. Platelet transfusions used in operating theatres were quantified, but data on product type and indications were not collected in the PLOT-ICU study [4, 29].

Bleeding

Bleeding was graded in four grades according to a modified World Health Organization (WHO) bleeding classification (details available elsewhere [4, 29] and in the supplement): grades 1 and 2 were smaller bleedings not requiring RBC transfusion; grade 3 bleeding was bleeding requiring up to two RBC transfusions and central nervous system (CNS) bleeding without symptoms; grade 4 bleeding was defined as bleeding requiring either (1) more than two RBC transfusions, (2) intubation and mechanical ventilation or (3) surgical intervention. Bleeding from critical sites (e.g., CNS bleeding) with symptoms and fatal bleedings were also considered grade 4 bleeding. Bleedings occurring in the operating theatres only were not assessed in the PLOT-ICU study [4, 29].

Data and variables

The PLOT-ICU study collected routine patient data from medical records; baseline data were collected at ICU admission and included demographics, comorbidities, selected treatments, illness severity (Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), an illness severity score ranging from 0–42 points with higher scores indicating higher predicted 90-day mortality [31, 32]), presence of bleeding and selected biochemistry. Data on bleeding events, thrombotic events, the use of blood products and platelet counts were collected daily during the ICU stay. Vital status was assessed on day 90 [4, 29].

We will use the following variables from the PLOT-ICU database to describe patient characteristics and outcomes (definitions are available elsewhere [4, 29] and in the supplement):

Baseline variables

- Age
- Sex
- Comorbidities
    - Chronic pulmonary disease
    - Ischaemic heart disease or heart failure
    - Chronic renal failure
    - Chronic liver failure
    - Haematological malignancy
    - Solid tumour cancer
    - Immunosuppression
    - Previous thrombo-embolism
- Days in the hospital prior to ICU admission
- Surgery prior to ICU admission
- Source of ICU admission
    - Emergency department or prehospital setting
    - Hospital ward
    - Operating or postoperative recovery room
    - Another ICU
- Primary reason for ICU admission
    - Neurological
    - Respiratory
    - Circulatory
    - Trauma
    - Haemorrhage
    - Other
- Treatments
    - Haematopoietic stem cell transplantation within one year prior to ICU admission
    - Chemotherapy within six weeks prior to ICU admission
    - Treatment with anticoagulating agents (any dose) within 48 hours prior to ICU admission
    - Treatment with platelet inhibitors within 48 hours prior to ICU admission
- Septic shock at ICU admission
- Acute liver failure at ICU admission

- SMS-ICU
- Biochemistry
    - Platelet count
    - Haemoglobin
    - International Normalized ratio (INR)
- Bleeding within 24 hours of ICU admission (i.e., modified WHO grade 1-4 bleeding)
- Platelet transfusions within 24 hours prior to ICU admission

Daily variables

- Lowest platelet count
- Number of platelet transfusions, type of product, total volume, indication and platelet count before transfusion.
- Number of RBC transfusions
- Number of plasma transfusions
- WHO Grade 3 or 4 bleeding
- New thrombotic event

Follow-up variables

- Death within 90 days

Additional variables

We will seek to obtain data on the method of dosing platelet transfusions (fixed dosing vs. weight-based dosing) for each site in the PLOT-ICU study, and for sites using fixed dosing, also general data on the average platelet dose in apheresis-derived and a whole-blood-derived products issued by the local blood bank.

Outcomes

Primary outcome

The primary outcome will be the number of patients receiving platelet transfusion in the ICU reported according to the product received (apheresis-derived vs. pooled whole-blood-derived platelet transfusions).

Secondary platelet transfusion outcomes

- Volume (mL) per platelet transfusion
- Absolute post-transfusion platelet count increment for prophylactic platelet transfusions used in the ICU
- Timing of platelet transfusions (during which days were platelet transfusions used and how many platelet transfusions were used on these days)
- Number of sites using weight-based dosing vs. fixed dosing approach to platelet transfusion

Secondary clinical outcomes

- Number of patients receiving at least one RBC transfusion
- Number of patients receiving at least one plasma transfusion
- Number of patients with at least one WHO grade 3 or 4 bleeding event in the ICU
- Number of patients with at least one new thrombotic event in the ICU
- Number of patients who died within 90 days from ICU admission

Statistical considerations

Sample size

The PLOT-ICU cohort study has a finite sample size of 1166 patients, of whom, 504 (43.2%) patients with thrombocytopenia will be eligible for this study [4].

Statistical considerations and reporting

We plan to present all data descriptively without formal statistical testing. Categorical data will be summarised with numbers and percentages and continuous data with medians and interquartile ranges (IQR). The primary outcome will be calculated as the number of patients receiving at least one platelet transfusion in the ICU and reported according to the type of product received; patients receiving both products will be counted in both categories. The result will be reported overall and stratified by country in countries with at least 10 transfused patients in a supplement to the manuscript. Volumes per platelet transfusion will be calculated from daily totals; the number of platelet transfusions divided by the total volume transfused. Post-transfusion platelet count increments for prophylactic platelet transfusions administered as single transfusions in the ICU will be calculated as the difference between the latest platelet count prior to transfusion and the lowest platelet count the next day. We will summarise results for volume per platelet transfusion and post-transfusion platelet count increments overall and stratified by countries with at least 10 platelet transfusions in a supplement to the manuscript as platelet dose and volume contained in a single platelet transfusion may vary.

We plan to describe the use of platelet transfusions relative to time since ICU admission graphically (e.g., by using a heatmap).

Characteristics at ICU admission and secondary clinical outcomes will be stratified on platelet transfusions status (i.e., those who did and did not receive platelet transfusion in the ICU) and on severity of thrombocytopenia (platelet count $<50x10^9$/L) as patients with severe thrombocytopenia received most of the platelet transfusions in the PLOT-ICU study [4].

Sensitivity analyses

To account for the loss of platelets during bleeding and surgery, we will reassess the post-transfusion platelet for count increments for prophylactic platelet transfusions excluding transfusion episodes where surgery or bleeding were registered on the day of transfusion or the day after.

Missing data

We will report missing data with numbers and percentages. Some patients were transferred directly from participating ICUs to non-participating ICUs where data for daily variables (clinical events, platelet counts etc.) were not obtainable (28/1166 patients in the entire cohort)[4]. In these cases, we will assume that no events occurred during the days spent in the non-participating ICU as done previously [4, 29].

Discussion

Thrombocytopenia is common in ICU patients [1, 2, 4] and may increase the risk of major bleeding complications[6]. Consequently, many ICU patients receive prophylactic platelet transfusion to reduce the risk of bleeding or cover invasive procedures [3, 4, 8, 12]. Recently, some evidence from a RCT has emerged regarding platelet transfusion before CVC placement[25], but these transfusions are quite rare in the general ICU population; we recently observed that platelet transfusions before invasive procedures or surgery constituted less than 10% of the platelet transfusions used in the ICU. Most transfusions (64%) were used for prophylaxis [4], for which the evidence from RCTs in the ICU setting is lacking. In the absence of randomised data, current guidelines are founded on indirect evidence from trials in the haemato-oncological setting and observational data [27]. Platelet transfusions are expensive, limited and not risk-free. RCTs evaluating prophylactic platelet transfusions are highly warranted to ensure safe and thoughtful use of this scarce resource in the ICU. This sub-study will provide international, contemporary data on important aspects of the epidemiology of platelet transfusions in adult thrombocytopenic ICU patients, describe potential differences across countries, and assess the characteristics and outcomes of those who received platelet transfusion in the ICU and those who did not. These data will, in turn, inform the planning of future platelet transfusion trials in the ICU setting.

This study will have some limitations. First, the study was planned *post hoc,* and the results should be considered exploratory. Second, data collection in the PLOT-ICU study was limited to the time spent in participating ICUs and events occurring outside these units were not accounted for. Third, the level of detail in this study will reflect the data structure in the PLOT-ICU database. For instance, the number and volume of blood products transfused were collected as daily totals which limits precision in calculations of individual platelet transfusion volumes. In addition, the temporal resolution in the PLOT-ICU database is confined to calendar days without exact time points of platelet transfusions and subsequent platelet count measurements. This should be considered when interpreting the results on platelet count increments as the time elapsed from transfusion to platelet count measurement may affect the increment [33, 34]. The PLOT-ICU database does not contain data on platelet doses of the individual transfusions and calculation of corrected platelet count increments (corrected for patient body surface area and platelet doses) will not be feasible.

The main strength of the study will reside in the large, unselected, multinational ICU population and the completeness and quality of the data and the results will likely be generalisable to many Nordic-, European- and American healthcare systems.

Conclusions

In summary, the present *post hoc* sub-study will provide additional contemporary international, epidemiological data on the use of platelet transfusions in adult acutely admitted ICU patients with thrombocytopenia, describe potential differences across countries and assess characteristics and outcomes among those receiving platelet transfusion in the ICU vs. those not receiving platelet transfusion. This will inform much-needed randomised trials evaluating the safety and efficacy of platelet transfusion in the ICU setting.

Publication policy

We will submit the results of this sub-study to an international peer-reviewed journal. The manuscript will be drafted following the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement and a completed checklist will be made available in a supplement to the manuscript [35]. Deviations from the protocol will be described and motivated.

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