Platelet transfusions and patient outcomes after cardiac surgery

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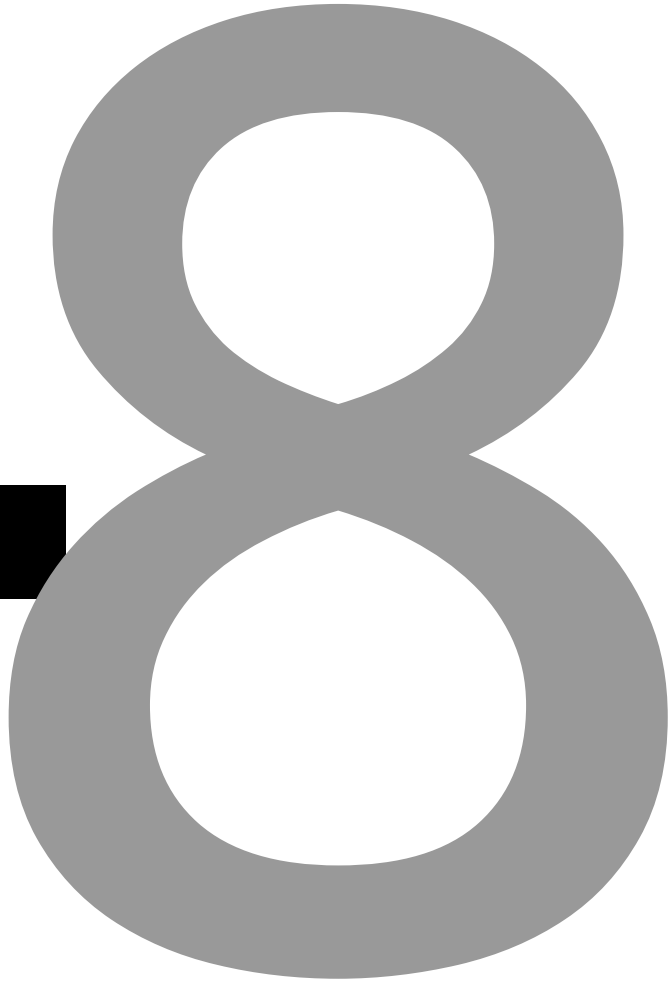
CHAPTER 8



Summary

Platelet transfusions are used to provide hemostatic capacity to patients with decreased number or functionality of platelets. The aim of this thesis was to expand knowledge about the safety and efficacy of platelet transfusions in general and in particular in cardiac surgery patients. In the decision to transfuse a patient with platelets, like in every clinical decision, it is important to weigh the potential benefits against the potential harm this treatment can cause. Therefore, we aimed at gaining more knowledge about potential harms and benefits for recipients of a platelet concentrate, and the storage medium and storage time of platelet concentrates. Expansion of knowledge about this topic can help clinicians to decide which patients to transfuse with platelets at which moment and to create possibilities to improve the safety and efficacy of platelet transfusions.

In the Netherlands most platelet concentrates are prepared using five buffy coats from whole blood donations (pooled platelets concentrates). These buffy coats are then resuspended either in 30-40% plasma and 60-70% platelet additive solution (PAS) (PAS-platelets) or, until April 2018, in 100% plasma of one of the five donors (plasma-platelets). In hematology patients, it has been described that reducing the amount of plasma in platelet units lowers the incidence of transfusion reactions. However, the results of these studies may not be applicable to other patients receiving platelet transfusions, like trauma or cardiac surgery patients. In our nationwide study, in **chapter 2**, covering a 10-year period with more than half a million platelet transfusions, we showed that PAS-C-platelets are associated with less transfusion reactions than plasma-platelets and PAS-B platelets.

Besides safety also efficacy is important to consider when comparing PAS-platelets with plasma-platelets. It is unclear whether PAS-platelet concentrates are as effective as plasma-platelet concentrates. A previous *in vitro* study, comparing platelets stored in different types of PAS with plasma-platelets, demonstrated inferior results for PAS-platelets compared to plasma-platelets. However, in this study testing was performed in the absence of red blood cells and blood plasma. Moreover, the correlation between the analyzed in-vitro endpoints and clinically relevant endpoints has not been established. The clinical studies analyzing the effectiveness of PAS-platelet transfusions have been performed in hematologic patients and have shown conflicting results. The results of these previous studies are possibly not applicable to surgical and trauma patients. In our *in vitro* study, we compared the hemostatic function of PAS-platelets to plasma-platelets in reconstituted whole blood using Multiplate-derived platelet aggregation, thromboelastography-measured overall clot formation and CD62P responsiveness. These tests are reported to correlate well with clinically relevant outcomes. As described

in **chapter 3**, we observed that the (Multiplate-derived) aggregation and the agonist induced CD62P responsiveness of PAS-C-platelets was lower than that of plasma-platelets. However, TEG-derived clot formation, showed no differences between the PAS-C-platelets and plasma-platelets.

Besides storage medium also the storage time of platelet concentrates is of interest for the safety and efficacy of platelet transfusions. Storage time has been associated with the accumulation of biological response modifiers, such as inflammatory cytokines and chemokines. Whether these changes have clinical consequences is not clear yet, as published results are contradictory. In our study, in **chapter 4**, we demonstrated that longer storage time is associated with a higher incidence of transfusion reactions in PAS-platelets. In plasma-platelets storage time showed no association with transfusion reaction rates. However, the overall incidence of transfusion reactions, so regardless of storage time, following plasma-platelets is higher than that of PAS-C-platelets. In our *in vitro* study, in **chapter 3**, (Multiplate-derived) aggregation and (TEG-derived) initial clot formation significantly declined with increasing storage time both in plasma-platelets and in PAS-platelets. Yet, (TEG-derived) maximum clot strength and clot growth rate did not decline with increasing storage time.

In addition to the characteristics of the platelet concentrate it is likely that patient characteristics and the specific clinical situation influence the efficacy of a platelet transfusion. Since a significant part of platelet transfusions is consumed by cardiac surgery patients, it is important to understand the impact of a platelet concentrate and its storage conditions on cardiac surgery patients. There is a lack of clinical evidence establishing the hemostatic effect of platelet transfusions in cardiac surgery patients. In addition, conflicting results have been reported regarding the safety of platelet transfusions in the setting of cardiac surgery. So, there is an unmet need to determine the clinical impact (safety and efficacy) of perioperative platelet transfusions in patients undergoing cardiac surgery. To the best of our knowledge, our study in **chapter 5** was the first describing not only the adverse outcomes, but also the intended effects of a platelet transfusion in cardiac surgery patients and thereby presenting an overall picture of the outcomes following platelet transfusion. We selected patients who received one platelet concentrate (and no other blood products) shortly after cardiopulmonary bypass (CPB). These patients were matched 1:3, based on propensity score, to patients who did not receive any blood products shortly after CPB. In this retrospective analysis, cardiac surgery patients receiving platelet transfusion in the operating room experienced less blood loss, but more often required vasoactive medication, prolonged ventilation, prolonged intensive care admission, and transfusion of other blood products postoperatively. Moreover, early platelet transfusion was not associated with reinterventions, thromboembolic complications, infections, multi-organ failure, or mortality.

During storage platelets undergo multiple changes in structure and function collectively known as the "platelet storage lesion". It is conceivable that in patients this "platelet storage lesion" results in a reduced hemostatic capacity and more adverse events. Subsequently, the question arose whether these "platelet storage lesions" have clinical consequences. In our study, described in **chapter 6**, in cardiac surgery patients we found that transfusion of old platelets was associated with a higher in-hospital mortality when compared to transfusion of fresher platelets. Moreover, patients transfused with old platelets more often suffered from blood loss of 1000 mL or more (in the first 12 hours after surgery) and more often required reoperation for bleeding than patients transfused with fresh platelets.

In **chapter 7** the main conclusions of this thesis are described and discussed. In this thesis we concluded that cardiac surgery patients receiving an early platelet transfusion experienced less blood loss than patients who did not receive an early platelet transfusion. However, early platelet transfusion was not associated with more reinterventions, thromboembolic complications, infections, multi-organ failure, or mortality. Furthermore, we concluded that PAS-C as storage medium for platelets is associated with more favorable outcomes than plasma with regard to transfusions reactions, but not with regard to *in vitro* hemostatic measurements. Furthermore, we concluded that fresh platelet concentrates are associated with more favorable outcomes than older platelet concentrates: less transfusions reactions in the whole transfused population, better hemostatic measurements *in vitro*, and less blood loss and mortality in cardiac surgery patients.